DISSERTATION
ON

A STUDY ON NEUROPSYCHIATRIC MANIFESTAIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Submitted in partial fulfilment of requirements for the degree of

D.M. NEUROLOGY (BRANCH-I)

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CERTIFICATE

This is to certify that this dissertation entitled **"A study on Neuropsychiatric Manifestations of Systemic Lupus Erythematosus"** submitted by **Dr. G. VIKRAMRAJ** appearing for **D.M. Neurology** Degree (Branch - I) examination in **August 2010** is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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DECLARATION

I solemnly declare that the dissertation titled **"A study on Neuropsychiatric Manifestations of Systemic Lupus Erythematosus"** is done by me at the Institute of Neurology, Madras Medical College & Govt. General Hospital, Chennai, during **2009-2010** under the guidance and supervision of **Prof. R.M. Bhoopathy**.

The dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of **D.M. Degree in Neurology.**

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CONTENTS

INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases. It affects predominantly women in their reproductive years. Remissions and relapses characterize the disease. The clinical manifestations and their severity in individual patients may vary considerably and, therefore, the treatment strategy needs to be tailored accordingly.[1,2,3,4.]

Systemic lupus erythematosus (SLE) has frequent and potentially serious neuropsychiatric (NP) manifestations that are of importance in the management of the disease. Lack of a diagnostic gold standard and ambiguous terminology have hampered epidemiologic research in neuropsychiatric systemic lupus erythematosus (NPSLE). The reported prevalence of NPSLE varies widely, from 14% to 75%, because of inconsistent classifications and selected patient populations in tertiary referral centers. A nomenclature system recently developed by the American College of Rheumatology (ACR) is the first step toward standardized and internationally accepted classification of NPSLE.[1,4,5,6,7.] This nomenclature comprises case definitions including diagnostic criteria, exclusions, and methods of ascertainment for a total of 19 syndromes.[50] The purpose of this cross-sectional, hospital based study is to assess the validity of the ACR nomenclature and case definitions for NPSLE.

AIMS AND OBJECTIVES

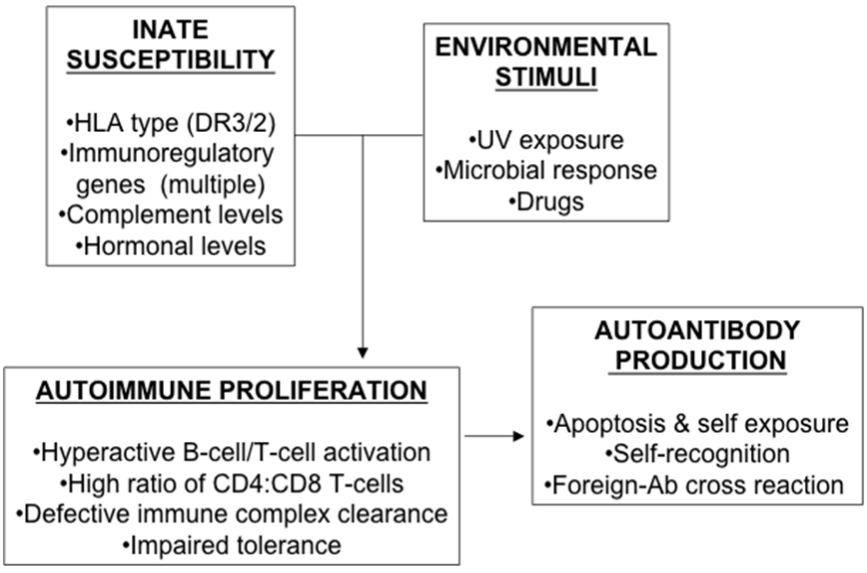
1. To study the Prevalence of Neuropsychiatric manifestations among SLE patients admitted in Government General Hospital, Chennai.
2. To categorize and study the prevalence of the different Neuropsychyatric syndromes described by American College of Rheumatologists' nomenclature.
3. To study the prevalence of Peripeheral Nerve disorders among these patients by electrophysiology.

REVIEW OF LITERATURE

Systemic lupus erythematosus (SLE) is a chronic, multifaceted inflammatory disease that can affect every organ system of the body. SLE is protean in its manifestations and follows a relapsing and remitting course.[1,2]

Pathophysiology

SLE is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors. Many immune disturbances, both innate and acquired, occur in SLE.[9,10]



In systemic lupus erythematosus (SLE), many genetic-susceptibility factors, environmental triggers, antigen-antibody responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity

One proposed mechanism for the development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance. The redistribution of cellular antigens during apoptosis leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. Thus, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens.[9]

Immune complexes form in the microvasculature, leading to complement activation and inflammation. Moreover, antibody-antigen complexes deposit on the basement membranes of skin and kidneys. In active SLE, this process has been confirmed based on the presence of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites. Serum antinuclear antibodies (ANAs) are found in virtually all individuals with active SLE, and antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE.

Frequency – International:

Worldwide, the prevalence of SLE varies. Although the prevalence of SLE is high in black persons in the United Kingdom, the disease is rarely reported among blacks who live in Africa. According to a recent report from the National Arthritis Data Working Group, approximately 250,000 Americans have systemic lupus.[4,6,7]

India: SLE is rare in India. A prevalence study in India (carried out in a rural population near Delhi) found a point prevalence of 3 per 100,000. This is a much lower figure than reported from the west (varying from 12.5 per 100,000 adults in England to 39 per 100,000 in Finland and 124 per 100,000 in USA). However, a fair number of cases of SLE are encountered in any large hospital in India. The incidence of SLE has tripled in the past 40 years, mainly as a result of improved diagnosis of mild disease.[5]

Mortality/Morbidity

The natural history of SLE varies from relatively benign disease to rapidly progressive and even fatal disease. SLE often waxes and wanes in affected individuals throughout life, and features of the disease vary greatly between individuals. The disease course is milder and survival rate higher among persons with isolated skin and musculoskeletal involvement than in those with renal and CNS disease.[4]

SLE carries an average 10-year survival rate that now exceeds 90%. Prior to 1955, the 5-year survival rate was less than 50%. Decreased mortality rates associated with SLE can be attributed to earlier diagnosis (including milder cases), improvement in disease-specific treatments, and advances in general medical care. According to the CDC, one third of SLE-related deaths in the

United States occur in patients younger than 45 years, making this a serious issue despite declining overall mortality rates. In 1976, Urowitz first reported bimodal mortality in early versus late SLE, noting that SLE-related deaths usually occur within the first 5-10 years of symptom onset.[12]

Infectious complications related to active SLE and immunosuppressive treatment are now the most common cause of death in early active SLE, and accelerated arteriosclerosis is a key cause of late mortality. The Framingham Offspring Study demonstrated that women aged 35-44 years with SLE were 50 times more likely to develop myocardial ischemia than healthy women. [11,12]

Sex: SLE frequently starts in women of childbearing age, and the use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease. The risk of SLE development in men is similar to that in prepubertal or postmenopausal women.[4]

Age: A correlation between age and incidence of SLE mirrors peak years of female sex hormone production. The prevalence of SLE is highest among women aged 14-64 years. SLE does not have an age predilection in males.[4]

Diagnosis of SLE

The American College of Rheumatology has a criteria for the classification of patients as having SLE. If a patient has, at any time in his or her medical history, 4 of the 11 criteria documented (Table below), the diagnosis of SLE can be made with about 95% specificity and 85% sensitivity.[5,13]

Revised ACR classification criteria for SLE (1997 update) [13]

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight by history or on physical exam.
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Non-erosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
Pleuritis/pericarditis	a.Pleuritis- convincing h/o pleuritic pain or rub or pleural effusion on physical examination OR b.Pericarditis- documented by ECG, rub or e/o effusion
Renal disorder	a. Persistent proteinuria > 0.5 gm/day or > +++, OR b. Cellular casts- may be red cell, Hb, granular, tubular or mixed
Neurological disorder	a. Seizures- in the absence of offending drugs, or known metabolic derangement, e.g. uraemia, ketoacidosis or electrolyte imbalance, OR b. Psychosis- in the absence of offending drugs, or known metabolic derangement, e.g. uraemia, ketoacidosis or electrolyte imbalance
Haematological disorder	a. Haemolytic anaemia with reticulocytosis, OR b. Leukopaenia < 4000/cu mm on 2 or more occasions, OR c. Lymphocytopenia < 1500 on 2 or more occasions, OR d. Thrombocytopenia < 100,000/cu mm in the absence of offending drugs
Immunological disorder	a. Anti-DNA: antibody to native DNA in abnormal titre, OR b. Anti-Sm: presence of antibody to Sm nuclear antigen, OR c. Positive finding of aPL antibodies based on: 1) ↑ serum level of IgG or IgM aCL or 2) a positive test result for lupus anticoagulant, using a standard method, or 3) a false-positive test for syphilis for at least 6 months and confirmed by TPI or FTA-abs test
Positive ANA	An abnormal titre of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drug

Serology in SLE

Since SLE is associated with a number of autoantibodies, it is important to understand their relevance in clinical practice. Some of these are useful as diagnostic markers, others help in quantifying disease activity and still others are primarily of research interest, making no contribution to patient care. A brief discussion follows:

Antinuclear antibody (ANA):

ANA is a good screening test for SLE because 95% of cases show a high titre (1:80 or more) of this autoantibody. A negative test result makes the diagnosis highly improbable. ANA may be positive in other rheumatic disorders such as systemic sclerosis, Sjogren's syndrome, overlap syndrome, antiphospholipid syndrome, polymyositis and rheumatoid arthritis. Like the rheumatoid factor test, ANA may also be positive in chronic infections, malignancies and in normal individuals. Thus, the specificity of ANA for diagnosis of SLE is quite low (app. 40% only). Performing serial titres of ANA in a diagnosed case of SLE is of no clinical value because it does not correlate well with disease activity.[5,15]

ANAs are actually a family of autoantibodies, which may be directed against any one of the following nuclear antigens: 1. Double stranded-DNA, 2. Extractable nuclear antigens (ENA), 3. Histones, 4. Nuclear RNA.[5]

Anti-double stranded DNA antibody (anti-dsDNA):

This test has high specificity for SLE. The positivity of anti-dsDNA in SLE at the time of presentation is in the range of 60% (although the cumulative positivity during the course of disease may approach 90%). Hence, anti-ds DNA can not be a good screening test for SLE. When positive, the test establishes the diagnosis of SLE. The anti-dsDNA titres most often correlate with disease activity.[17]

The classic finding of a low C-reactive protein (CRP) level but an elevated erythrocyte sedimentation rate (ESR) or plasma viscosity was seen in about 40% of patients. In previously undiagnosed patients thought to have SLE, the principal diagnostic study is the antinuclear antibody (ANA) test.

Although many rheumatologists consider this test to be 100% sensitive for diagnosis, a positive ANA result alone is not sufficient for diagnosis. Positive test results are seen in other autoimmune conditions and in a certain percentage of the general population (especially the elderly). Anti-DNA antibody testing is positive in only about 70% of CNS episodes.

When a positive ANA result is thought to be clinically relevant, follow up with an antibody to native, double-stranded DNA (dsDNA antibody) to confirm the diagnosis of SLE. An autoantibody panel should be checked for related pathogenic antibodies.[5,20]

Of particular interest are the serum antiribosomal P antibody (which is positive in 60% of cases of lupus psychosis) and the family of antibodies known collectively as antiphospholipid antibodies (including the anticardiolipin antibody, [ACLA]). These may be positive in hypercoagulable states, myelopathy, and LSE. APA were present in 16-60% of the reported cases.

Complement studies (C3, C4, CH50) may be useful to determine disease activity in patients known or thought to have SLE.

Antiphospholipid syndrome was first described in association with SLE but also may occur independently. This should be searched for in patients with known to have SLE with neurologic complications, especially myelopathy or cerebrovascular events, whether embolic, thrombotic, or hemorrhagic. Concomitant SLE and antiphospholipid syndrome has been shown to increase the risk of nervous system involvement.

In addition to testing serum ACLA, hematologic studies may reveal a circulating anticoagulant (originally called the lupus anticoagulant). Prolongation of the activated partial thromboplastin time (aPTT) only identifies 30% of circulating anticoagulants. Sensitivity may be enhanced by the Russell viper venom test, the kaolin clotting time, or variations using hexagonal phase phospholipids or other adsorbents.

CSF abnormalities were seen in 30-40% of patients reported. The frequency of CSF oligoclonal bands has varied between reports, lower range generally around 20%. An abnormal CSF is generally associated with a poor prognosis. Cerebrospinal fluid (CSF) examination is most useful to exclude infection, especially in immunocompromised patients. However, CSF can reflect increased CNS lupus activity by showing elevated levels of white cells, protein, immunoglobulin synthesis, or absolute immunoglobulin G (IgG). Antineuronal nuclear antibodies (ANNA) have some value in confirming CNS disease when performed on CSF but are less specific or sensitive than a serum test.[4,5]

Conventional blood studies have varying utility in diagnosing SLE, depending on associated conditions and manifestations.

Electrolytes, glucose, and calcium are especially worth checking in the setting of new-onset generalized seizures or acute encephalopathy. Acid-based disturbances may be obvious on review of electrolytes, but an arterial blood gas analysis may be useful to assess or follow such a disturbance, especially in the obtunded, acutely ill patient.

Lupus nephritis activity is customarily followed by assessing casts in the urine and proteinuria measured by dipstick or 24-hour collection but may be followed more roughly by the BUN and creatinine levels. Acute increases in

BUN may produce metabolic encephalopathy, but on a chronic basis, very high BUN elevations may be surprisingly well tolerated.

The CBC in SLE may demonstrate a hemolytic anemia with reticulocytosis or reductions of neutrophils, lymphocytes, or platelets.

Muscle enzyme levels (creatine kinase, aldolase) may be moderately or severely elevated with lupus myopathy, although normal levels also may be seen with clinical or biopsy-proven disease. Normal creatine kinase levels, therefore, do not reliably distinguish between SLE myositis and drug-related (steroid, hydroxychloroquine) myopathy.[24]

Imaging Studies

Joseph et al (2007) in their study have reported that 35% of CT brain scans were abnormal and 65% of MR scans, but CT remains valuable in identifying hemorrhages and larger infarcts. Neuroradiologic evaluation favors MRI over CT scans because subtle ischemia or cerebritis may be seen with greater sensitivity. The most common findings with either study are ischemic zones that may correspond to cortical or subcortical infarcts and may be large or small according to the size of vessel involved and the mechanism of stroke. See the image below for an example of ischemia visible on MRI.[27]

Other vague areas of patchy cortical or subcortical abnormality (lucency on CT, T2 signal intensity on MRI) may correspond to small vessel vasculitis or

cerebritis, but distinction from opportunistic infection (eg, toxoplasmosis, progressive multifocal leukoencephalopathy) often cannot be made on radiographic grounds, requiring other studies, including cerebral biopsy. With either CT or MRI, contrast enhancement increases the sensitivity for acute and subacute cerebral lesions.[28]

A frequent clinical problem occurs when the MRI reveals multiple small T2 signal intensities in the white matter, making it difficult to distinguish between multiple sclerosis and SLE or other vasculitides. Although many clinical and laboratory factors assist in this differential diagnosis, the MRI appearance is more supportive of SLE when the lesions are not confined to periventricular white matter but favor the gray-white junction or even involve gray matter of cortex or deep nuclei when the lesions are rounded or patchy in shape. If the lesions are radially oriented along white matter tracts, favor the periventricular white matter, and involve the corpus callosum, then multiple sclerosis is a more likely diagnosis.[27,28,29]

Perisulcal cortical atrophy is reported as a frequent finding on CT.

CT scanning may detect calcifications in patients with long-standing cerebritis.

Dural sinus thrombosis is a rare complication of SLE-associated hypercoagulability and is often seen in association with antiphospholipid

antibodies. Radiologically, flow defects in one or more venous sinuses may be imaged on MRI, MR venous angiography, conventional angiography, or radionuclide brain scan. Associated edema or hemorrhagic infarcts may be obvious on MRI or CT scans.

PET scanning and magnetic resonance spectroscopy (MRS) promise greater sensitivity for cerebritis. However, the greatest utility of imaging studies remains the exclusion of unexpected mass lesions or opportunistic infectious processes.

When embolic stroke occurs in patients with proven or suspected SLE, echocardiography is mandatory to assess for valvular and other intracardiac lesions. In the patient known to have SLE who presents with an apparently nonembolic stroke syndrome or apparent so-called focal cerebritis, cardiac emboli remain the most likely etiology, mandating echocardiography in these settings as well. Transesophageal echocardiography may be helpful in selected cases.[29]

Strokes and leukoaraiosis were more common in the APLS group, consistent with the idea of an APLS-induced prothrombotic state.

The carotid bifurcation may be conveniently imaged by ultrasound.

Magnetic resonance angiography (MRA) or transcranial Doppler ultrasound confirm thrombotic lesions of extracranial or intracranial vessels.

Cerebral vasculitis can only be detected by conventional contrast angiography. However, even this study often misses the predominantly small vessel involvement of lupus vasculopathy.

In patients with SLE who have myelopathy, spinal MRI or myelography is mandatory to exclude compressive lesions. MRI also may demonstrate intramedullary spinal lesions, with variable sensitivity that depends on imaging sequences and technical factors related to the MRI equipment. If myelography is elected, CSF should be obtained prior to contrast introduction to assess for SLE disease activity, cytology, or evidence of opportunistic infection as appropriate.[29]

Other Tests

Electroencephalography (EEG) may be helpful to confirm the focal point of an apparently diffuse encephalopathy. It is most useful in patients with seizures whose cases are difficult to manage.

EEG also provides a measure of recurrence risk when anticonvulsant therapy is withdrawn. An active spike focus (especially with multiple loci), frequent discharges, or localization to the frontotemporal region predicts a likely recurrence of seizures after anticonvulsant cessation. A normal EEG, even with sleep deprivation, does not exclude the possibility of recurrent seizures. It generally is associated with a reduced recurrence risk, although this

has not been studied specifically in CNS lupus.[30] Reported selective left temporolimbic region changes are not always observed.

EMG and nerve conduction studies (NCS) provide useful data in the clinical assessment of peripheral complications of SLE.

Muscle weakness in patients with SLE may result from inflammatory myopathy, medication-induced myopathy, neuromuscular junction dysfunction, neuropathies, or from other musculoskeletal disturbances. While much of the clinical decision-making relies on examination and historical evidence (especially time course of drug therapy with steroids or hydroxychloroquine), EMG may be useful in distinguishing inflammatory from noninflammatory myopathy.

Lupus myositis resembles dermatomyositis or polymyositis on EMG findings, including increased insertional activity, fibrillations and positive sharp waves, and myopathic motor unit potentials and recruitment patterns, as well as complex repetitive discharges. Lupus myositis may present with normal EMG findings, especially (but not exclusively) if partially treated, so that a normal needle examination does not exclude inflammatory myositis in SLE.

Repetitive stimulation studies may be used to search for neuromuscular junction pathology analogous to that seen with either myasthenia or myasthenic syndrome. (This is rare in SLE but has been reported.)

Peripheral nerve dysfunction in SLE presents clinically as mononeuritis multiplex, symmetrical distal polyneuropathy (sensory or sensorimotor), or acute demyelinating polyradiculopathy. The typical findings of each of these conditions may be demonstrated on conventional nerve conduction studies. As with other causes of acute polyradiculopathy, proximal nerve conduction studies or F and H wave studies may be needed to demonstrate proximal dysfunction, especially early in the course of the disease.

Procedures

Nerve biopsy may be helpful in determining an initial diagnosis of active vasculitis when clinical findings are ambiguous because of the relatively high yield of nerve biopsy in early clinical vasculitis. However, in many cases of clinically confluent, symmetric polyneuropathy, the predominant pathology may be nonspecific demyelination, reducing the clinical value of the procedure. When more than one potential etiology is present in the case of a disabling polyneuropathy, biopsy may determine the predominant pathology, serving as a potential alternative to empiric treatment for one or more etiologies.

Muscle biopsy may provide the only reliable differentiation between inflammatory and medication-induced myopathy.[41] Clinical evolution and medication history are most reliable, as creatine kinase is usually, but not always, elevated in inflammatory myopathy. EMG is usually, but not always,

abnormal in inflammatory myopathy, and both are usually normal in medication-induced myopathy. When other factors are ambiguous and empiric therapy is impractical, then muscle biopsy is appropriate. Brain biopsy and Meningeal biopsy are done in rare circumstances.

Histologic Findings

In nerve biopsies, active necrotizing vasculitis may involve epineurial arterioles. Often perivascular infiltrates are found without frank arterial necrosis. Immunofluorescent staining may demonstrate immunoglobulin or complement deposition on vessel walls.

At times, the only findings are nonspecific demyelination or nerve fiber dropout.

Muscle biopsy most commonly reveals similar findings, emphasizing vascular and perivascular inflammation, similar to the muscle pathology in dermatomyositis. Less frequently, a pathology analogous to classic polymyositis is found, with inflammatory and other changes centered more on the muscle fibers, including frank necrosis, phagocytosis, and degeneration and regeneration of type I and II fibers.

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)

NS lupus is a serious but potentially treatable illness, which, still presents very difficult diagnostic challenges. It is in the differential diagnosis for many neurological conditions. Neurologists need to be aware of the various presentations and neurologic complications of SLE, as patients with SLE often have neurologic symptoms and SLE is sometimes diagnosed after patients present for treatment of a neurologic event [4,5]

The prevalence of NPSLE ranges widely between 14 and 75%, reflecting variable diagnostic criteria and differences in selection of patients for study. The ACR has recently developed a standardized nomenclature system which provides case definitions for 19 NP syndromes seen in SLE, including reporting standards and recommendations for laboratory and imaging tests.[50]

The Neuropsychiatric syndromes in Systemis Lupus Erythematosus according to the American College of Rheumatology nomenclature and case definitions[5,50]

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculo-neuropathy
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia gravis
Movement disorder (chorea)	Neuropathy, cranial
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

1. **Acute confusional state (Delirium)**[50]

Disturbance of consciousness or level of arousal characterized by reduced ability to focus, maintain, or shift attention, and accompanied by disturbances of cognition, mood, affect, and/or behavior. The disturbances typically develop over hours to days and tend to fluctuate during the course of the day. They include hypo- and hyperaroused states and encompass the spectrum from delirium to coma.

Diagnostic criteria:

Disturbance of consciousness or level of arousal with reduced ability to focus, maintain, or shift attention, and one or more of the following developing over a short period of time (hours to days) and tending to fluctuate during the course of the day:

a. Acute or subacute change in cognition that may include memory deficit and disorientation.

b. A change in behavior, mood, or affect (e.g., restlessness, overactivity, irritability, apathy, anxiety, mood lability, etc.).

Exclusions:

- Primary mental/neurological disorder not related to SLE.
- Metabolic disturbances (including glucose, electrolytes, fluid, osmolarity).
- Substance or drug-induced delirium (including withdrawal).
- Cerebral infections.

2. **Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)**[50]

Diagnostic criteria:

a. Clinical features

i. Progressive polyradiculoneuropathy, usually ascending and predominantly motor, which peaks usually within 21 days or less.

ii. Reflex loss.

iii. Symmetric, may involve the trunk and may cause respiratory failure.

b. Cerebrospinal fluid(CSF) i. Increased CSF protein without pleocytosis.

c. Supportive evidence by nerve conduction study including F-wave ascertainment whereby there is one abnormality in three nerves. The abnormalities are:

i. Conduction block in which the amplitude of compound muscle action potential diminishes with more proximal sites of nerve stimulation.

ii. F waves may be absent or prolonged.

iii. Slowing of conduction velocity.

iv. Prolongation of distal latencies.

Exclusions:

- Acute spinal cord disease.
- Botulism.
- Poliomyelitis and other infections.
- Acute myasthenia gravis.

3. **Anxiety disorder**[50]

Anticipation of danger or misfortune accompanied by apprehension, dysphoria, or tension. Includes generalized anxiety, panic disorder, panic attacks, and obsessive-compulsive disorders.

Diagnostic criteria:

Both of the following:

a. Prominent anxiety, panic disorder, panic attacks, or obsessions or compulsions.

b. Disturbance causes clinically significant distress or impaired social, occupational, or other important functioning.

4. **Aseptic Meningitis**

Diagnostic criteria: All the following:

a. Acute or subacute onset of headache with photophobia, neck stiffness, and fever.

b. Signs of meningeal irritation.

c. Abnormal CSF.

5. **Autonomic disorder**[50]

Disorder of the autonomic nervous system with orthostatic hypotension, sphincteric erectile/ejaculatory dysfunction, anhidrosis, heat intolerance, constipation.

Diagnostic criteria:

Symptoms and abnormal response to provocative tests:

Test normal range

a. Blood pressure response to standing: fall in blood pressure more than 30/15 mmHg or vertical tilt (systolic/diastolic).

b. Heart rate response to standing: increases 11–29 beats/minute.

c. Heart rate variation with respiration: maximum–minimum heart rate: 15 beats/minute; E:I ratio (ratio of heart rate during expiration and inspiration): 1:2.

c. Valsalva ratio: 1:4.

d. Sweat test: Sweating over all body and limbs.

6. **Cerebrovascular disease**

Diagnostic criteria:

One of the following and supporting radioimaging study:

a. Stroke syndrome: acute focal neurological deficit persisting more than 24 hours (or lasting less than 24 hours with computed tomography (CT) or

magnetic resonance imaging (MRI) abnormality consistent with physical findings/symptoms.

b. Transient ischemic attack: acute, focal neurological deficit with clinical resolution within 24 hours (without corresponding lesion on CT or MRI).
c. Chronic multifocal disease: recurrent or progressive neurological deterioration attributable to cerebrovascular disease.
d. Subarachnoid and intracranial hemorrhage: bleeding documented by CSF findings, MRI/CT.
e. Sinus thrombosis: Acute, focal neurological deficit in the presence of increased intracranial pressure.

Note: The finding of unidentified bright objects on MRI without clinical manifestations is not classified at the present time.

7. **Cognitive Dysfunction:**[50] Significant deficits in any or all of the following cognitive functions: simple or complex attention, reasoning, executive skills (e.g., planning, organizing, sequencing), memory (e.g., learning and recall), visuospatial processing, language (e.g., verbal fluency), and psychomotor speed. Cognitive dysfunction implies a decline from a higher level of functioning and ranges from mild impairment to severe dementia. It may or may not impede social, educational, or occupational functioning, depending on

the function(s) impaired and the severity of impairment. Subjective complaints of cognitive dysfunction are common and may not be objectively verifiable. Neuropsychological testing should be done in suspected cognitive dysfunction, and its interpretation should be done with a neuropsychologist.

Diagnostic criteria:

a. Documented impairment in one or more of the following cognitive domains:

i. Simple attention.

ii. Complex attention.

iii. Memory (e.g., learning and recall).

iv. Visuospatial processing.

v. Language (e.g., verbal fluency).

vi. Reasoning/problem solving.

vii. Psychomotor speed.

viii. Executive functions (e.g., planning, organizing, and sequencing).

b. The cognitive deficits represent a significant decline from a former level of functioning (if known).

c. The cognitive deficits may cause varying degrees of impairment in social, educational, or occupational functioning, depending on the function(s) impaired and the degree of impairment.

8. **Demyelinating syndrome**[50]

Diagnostic criteria:

Two or more of the following, each occurring at different times, or one of the following occurring on at least two different occasions:

a. Multiple discrete areas of damage to white matter within CNS, causing one or more limbs to become weak with sensory loss.
b. Transverse myelopathy.
c. Optic neuropathy.
d. Diplopia because of isolated nerve palsies or internuclear ophthalmoplegia.
e. Brain stem disease with vertigo, vomiting, ataxia, dysarthria, or dysphagia.
f. Other cranial nerve palsies.

9. **Headache**

a. Migraine

i. Migraine without aura: Idiopathic, recurrent headache manifested by attacks lasting 4–72 hours. Typical characteristics are unilateral location, pulsating quality, moderate-to-severe intensity, aggravation by routine physical activity, and associated with nausea, vomiting,

photo- and phonophobia. At least five attacks fulfilling the aforementioned criteria.

ii. Migraine with aura: Idiopathic, recurrent disorder manifested by attacks of neurological symptoms localizable to cerebral cortex or brain stem, usually gradually developing over 5–20 minutes and lasting less than 60 minutes. Headache, nausea, and/or photophobia usually follow neurologic aura symptoms directly or after an interval of less than 1 hour. Headache usually lasts 4–72 hours, but may be completely absent.

b. Tension headache (episodic tension-type headache).

Recurrent episodes of headaches lasting minutes to days. Pain typically pressing/tightening in quality, of mild-to-moderate intensity, bilateral in location, and does not worsen with routine physical activity. Nausea is rare, but photophobia and phonophobia may be present. At least 10 previous headaches fulfilling these criteria

c. Cluster headache.

Attacks of severe, strictly unilateral pain, orbital, supraorbital, and/or temporal, usually lasting 15–180 minutes and occurring from at least once every other day up to eight times per day. Associated with one or more of the following: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and

facial sweating, miosis, ptosis, eyelid edema. Attacks occur in series for weeks or months ("cluster" periods), separated by remissions of usually months or years.

d. Headache from intracranial hypertension (also called pseudotumor cerebri, benign intracranial hypertension. All of the following:

i. Increased intracranial pressure (200 mm H2O) measured by lumbar puncture.

ii. Normal neurological findings, except for papilledema and possible nerve VI palsy.

iii. No mass lesion and no ventricular enlargement on neuroimaging.

iv. Normal or low protein and normal white cell count in CSF.

v. No evidence of venous sinus thrombosis.

e. Intractable headache, nonspecific.

10. **Mononeuropathy (single/multiplex)** [50]

Disturbed function of one or more peripheral nerve(s) resulting in weakness/paralysis or sensory dysfunction because of either conduction block in motor nerve fibers or axonal loss. Conduction block is related to demyelination with preservation of axon continuity. Remyelination may be rapid and complete. If axonal interruption takes place, axonal degeneration

occurs below the site of interruption and recovery is often slow and incomplete. Sensory symptoms and sensory loss may affect all modalities or be restricted to certain forms of sensation.

Diagnostic criteria:

a. Clinical demonstration of motor/sensory disturbances in the distribution of a peripheral nerve *and/or*

b. Abnormalities on nerve conduction studies or electromyogram (EMG) (i.e., concentric needle examination).

11. **Mood disorders**[50]

Prominent and persistent disturbance in mood characterized by:

- Depressed mood or markedly diminished interest or pleasure in almost all activities *or*
- Elevated, expansive or irritable mood.

Diagnostic criteria:

a. Major depressive-like episode.

One or more major depressive episodes with at least five of the following symptoms, including either i or ii or both, during a 2-week period and nearly every day:

i. Depressed mood most of the day, by subjective report or observation made by others. ii. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, by subjective report or observation made by others.

iii. *(1)* Significant weight loss without dieting or weight gain (>5% of body weight in 1 month).

(2) Insomnia or hypersomnia. Psychomotor agitation or retardation (observable by others, not merely subjective feeling of restlessness or being slowed down).

(3) Fatigue or loss of energy.

(4) Feelings of worthlessness or excessive or inappropriate guilt (may be delusional).

(5) Diminished ability to think or concentrate, or indecisiveness.

(6) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

b. Mood disorder with depressive features.

All of the following:

i. Prominent and persistent mood disturbance characterized by predominantly depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.

ii. Full criteria for major depressive-like episode are not met.

c. Mood disorder with manic features.

i. Prominent and persistent mood disturbance characterized by predominantly elevated, expansive or irritable mood.

d. Mood disorder with mixed features.

i. Prominent and persistent mood disturbance characterized by symptoms of both depression and mania; neither predominates.

For all mood disorders: Symptoms must cause significant distress or impairment in social, occupational, or other important areas of functioning.

12. **Movement disorder (chorea)** [50]

Chorea: Irregular, involuntary brief and unpredictable, jerky movements that may involve any portion of the body in random sequence

Diagnostic criteria:

Both of the following:

a. Observed abnormal movements.

b. Random, unpredictable sequence of movements.

13. **Myasthenia gravis** [50]

Neuromuscular transmission disorder characterized by fluctuating weakness and fatigability of bulbar and other voluntary muscles without loss of reflexes or impairment of sensation or other neurological function. Myasthenia gravis is an autoimmune disorder mediated by antibodies to acetylcholine receptors. It may occur with other diseases of immunological origin.

Diagnostic criteria:

a. Characteristic signs and symptoms include one or more of the following:

i. Diplopia, ptosis, dysarthria, weakness in chewing, difficulty in swallowing, muscle weakness with preserved deep tendon reflexes, and, less commonly, weakness of neck extension and flexion, and weakness of trunk muscles.

ii. Increased weakness during exercise and repetitive use with at least partially restored strength after periods of rest.

iii. Dramatic improvement in strength following administration of anticholinesterase drug (edrophonium and neostigmine).

And one or more of the following:

b. EMG and repetitive stimulation of a peripheral nerve: In myasthenia gravis, repetitive stimulation at a rate of two per second shows characteristic

decremental response that is reversed by edrophonium or neostigmine. Single-fiber studies show increased jitter.

c. Antibodies to acetylcholine receptors.

14. **Myelopathy**[50]

Diagnostic criteria:

Usually rapid onset (hours or days) of one or more of the following:

a. Bilateral weakness of legs with or without arms (paraplegia/quadriplegia); may be asymmetric.

b. Sensory impairment with cord level similar to that of motor weakness, with or without bowel and bladder dysfunction.

15. **Neuropathy, cranial**[50]

Diagnostic criteria:

Syndrome corresponding to specific nerve function:

a. Olfactory nerve: loss of sense of smell, distortion of smell, and loss of olfactory discrimination.
b. Optic nerve: decrease or loss of visual acuity, diminished color perception, afferent pupillary defect, and visual field deficits.

c. Oculomotor nerve: ptosis of the upper eyelid and inability to rotate eye upward, downward, or inward (complete lesion), and/or dilated nonreactive pupil and paralysis of accommodation (interruption of parasympathetic fibers only).
d. Trochlear nerve: extorsion and weakness of downward movement of affected eye.
e. Abducens nerve: weakness of eye abduction.
f. Trigeminal nerve: paroxysm of pain in lips, gums, cheek, or chin initiated by stimuli in trigger zone (trigeminal neuralgia) and sensory loss of the face or weakness of jaw muscles.
g. Facial nerve: unilateral or bilateral paralysis of facial expression muscles, or impairment of taste, or hyperacusis (painful sensitivity to sounds).
h. Vestibulo-cochlear nerve: deafness, tinnitus (cochlear), dizziness, and/or vertigo (vestibular).
i. Glossopharyngeal nerve: swallowing difficulty, deviation of soft palate to normal side, anesthesia of posterior pharynx and/or glossopharyngeal neuralgia (unilateral stabbing pain in root of tongue and throat, triggered by coughing, sneezing, swallowing, and pressure on ear tragus).
j. Vagus nerve: soft palate droop, loss of the gag reflex, hoarseness, nasal voice, and/or loss of sensation at external auditory meatus.

k. Accessory nerve: weakness and atrophy of sternocleidomastoid muscle and upper part of trapezius muscle.

l. Hypoglossal nerve: paralysis of one side of tongue with deviation to the affected side.

16. **Plexopathy**[50]

Disorder of brachial or lumbosacral plexus producing muscle weakness, sensory deficit, and/or reflex change not corresponding to the territory of single root or nerve.

Diagnostic criteria:

All of the following:

a. Characteristic signs and symptoms:

i. Brachial plexus: deep pain in shoulder, muscle weakness, sensory deficit and/or reflex impairment of arm, or

ii. Lumbosacral plexus: deep boring pain in thigh, muscle weakness, sensory deficit, and/or reflex impairment of leg.

b. Positive EMG finding (concentric needle examination) *and/or* nerve conduction studies for EMG: more than one root or nerve abnormalities with sparing of paraspinal muscles for nerve conduction study: absent or reduced amplitude on motor or sensory nerve conduction.

c. Normal MRI or CT scan (optional: myelogram) to rule out a higher neurological lesion.

17. **Polyneuropathy**[50]

Acute or chronic disorder of sensory and motor peripheral nerves with variable tempo characterized by symmetry of symptoms and physical findings in a distal distribution.

Diagnostic criteria:

One or both of the following:

a. Clinical manifestations:

i. Clinical demonstration of distal sensory and/or motor deficit.

ii. Symmetry of signs/symptoms, and/or.

b. Confirmation by EMG:

i. Concentric needle examination demonstrating denervation of muscle,

or

ii. Nerve conduction study demonstrating axonal or demyelinating neuropathy.

18. **Psychosis**[50]

Severe disturbance in the perception of reality characterized by delusions and/or hallucinations

Diagnostic criteria:

All of the following:

a. At least one of the following:

i. Delusions.

ii. Hallucinations without insight.

b. The disturbance causes clinical distress or impairment in social, occupational, or other relevant areas of functioning.

c. The disturbance does not occur exclusively during the course of a delirium.

d. The disturbance is not better accounted for by another mental disorder (e.g., mania).

19. **Seizures and seizure disorders**

Abnormal paroxysmal neuronal discharge in the brain causing abnormal function. Seizures are divided into *partial* and *generalized*. Partial seizures have clinical or electroencephalographic evidence of a focal onset; the abnormal discharge usually arises in a portion of one hemisphere and may spread to the rest of the brain during a seizure. Primary generalized seizures have no

interictal evidence of focal onset on electroencephalogram (EEG). A generalized seizure can be primary or secondary.

a. Primary generalized seizures (bilaterally symmetric and without local onset).

i. Tonic clonic (grand mal) or tonic or clonic.

ii. Atonic or astatic seizures.

iii. Absence seizures (petit mal).

iv. Myoclonic seizures.

b. Partial or focal seizures (seizures beginning locally) (also referred to as Jacksonian, temporal lobe, or psychomotor seizure, according to type).

i. Simple, without impairment of consciousness. (motor, sensory, aphasic, cognitive, affective, dysmnesic, illusional, olfactory, or psychological).

ii. Complex, with partial impairment of consciousness

iii. Simple or complex may evolve to secondary generalized tonic/clonic seizures.

Diagnostic criteria:

a. Independent description by a reliable witness.

b. EEG abnormalities

Treatment

Medical Care

Treatment of systemic lupus erythematosus (SLE) should be provided in cooperation with a consulting rheumatologist. Therapeutic intensity correlates with the severity of an acute attack. NSAIDs and other symptomatic agents are used for less threatening symptoms. Corticosteroids are used in low-dose oral, high-dose oral, or high-dose IV regimens according to the severity of potential organ damage.[4]

Clinical studies supporting this approach were generally performed in lupus nephritis because of its frequency, severity, and quantifiable improvement or deterioration, but the same treatment approaches are generally applied to other organ systems, including the central and peripheral nervous systems and muscular disease. This overall treatment approach should be familiar to neurologists who are accustomed to the evaluation and treatment of other autoimmune conditions such as multiple sclerosis, myasthenia gravis, or polymyositis.[5]

With little evidence base to the therapeutic modalities, a logical approach to the treatment of cerebral lupus is to build a treatment strategy around the various possible pathogeneses: (1) ischemia due to thromboses secondary to the

antiphospholipid syndrome, (2) small-vessel noninflammatory proliferative vasculopathy due to cell-mediated immune mechanisms, and (3) antibody-mediated damage to spinal cord and optic nerve—akin to Devic disease.[31]

The standard treatment for the non-thrombotic syndromes associated with SLE is immunosuppression, first with corticosteroids and with early recourse to cyclophosphamide. A *Cochrane Database Systematic Review* found no randomized controlled trials comparing these two treatments and concluded there was no evidence of a treatment advantage of cyclophosphamide.[32]

High-dose IV corticosteroid regimens consist of methylprednisolone 1-2 g daily for 3-6 doses, followed by oral prednisone 60 mg daily, then tapering according to clinical recovery. Less threatening flare-ups may be treated with as much as 100 mg or as little as 10 mg prednisone PO qd (or other agents in equivalent dosage), again tapering gradually according to clinical symptoms, with an increase of 10-20% during the taper if clinical disease flares again. Tapering to an every other day steroid regimen reduces adverse effects substantially but probably will not be successful until clinical disease is quite stable. In acute high dosage, steroids may provoke status epilepticus, psychosis, hypokalemia, hyperglycemia, or hypertension and clinical evidence of any intercurrent infection may be reduced.[4]

With chronic use, steroids cause familiar adverse effects including weight gain, diabetes mellitus, cataracts, immunocompromise, and osteoporosis. Calcium supplementation (1 g daily for men or premenopausal women, 1.5 g daily for postmenopausal women) should be initiated early and continued even when steroids are tapered successfully to qod.

The discovery that Toll-like receptor signaling and interferon-alpha abundance are central elements of the disease process has led to a new appreciation for hydroxychloroquine as an essential baseline medication. Modulation of the immune system via B-cell depletion is entering clinical practice. Mycophenolate mofetil is an effective and safer alternative to cyclophosphamide for patients with lupus nephritis. Other therapeutic approaches under development include anticytokine therapies, co-stimulatory blockade, antigen-specific immune modulation, and hematopoietic stem cell transplantation.[33]

Various steroid-sparing strategies have evolved for long-term use, including cyclophosphamide 0.5-2 mg/kg/d, azathioprine 1-2 mg/kg/d, and methotrexate 10-15 mg given once weekly with folate rescue, permitting gradual reduction or elimination of chronic steroid therapy. Higher dose ranges or dosing based on body surface area may be used for these medications based on the experience of individual clinicians.

All chronic cytotoxic regimens present substantial risks and should be followed only by physicians familiar with these agents. In acute, life-threatening illness, one option is to initiate cyclophosphamide PO or a single dose of 8-20 mg/kg IV, along with IV methylprednisolone.[1,4]

Jonsdottir et al (2008) reported that the majority of patients improved following rituximab plus cyclophosphamide.[34] The differential downregulation of anti-DNA of the IgG and IgA but not the IgM isotypes supports the hypothesis that cells producing pathogenic autoantibodies are preferentially targeted by the treatment. The fact that greater absolute numbers of $CD19^+$ cells at baseline predict a less impressive clinical and serological response suggests that more flexible dosing could be advantageous.

Antimalarials, especially hydroxychloroquine in dosage of 100-400 mg daily, are used as alternatives to steroids or as supplements to accelerate steroid taper. They have not been studied in central or peripheral nervous system disease. Antimalarials generally require months to become effective, and, therefore, they are not used in the acute treatment of organ-threatening disease.[35]

Generally, mild myopathy or polyneuropathy may be treated with NSAIDs and other symptomatic medications (eg, anticonvulsants, tricyclics, other medications used for neurogenic or musculoskeletal pain). Symptoms

may be caused by medications (eg, steroids, antimalarials) or other etiologies in addition to SLE. If alternative explanations are unlikely and symptoms are more bothersome, low-to-medium dose prednisone may be tried, possibly with a longer-term transfer to antimalarial therapy.[36]

If a patient with SLE presents with acute polyradiculopathy resembling Guillain-Barré syndrome or chronic relapsing polyradiculopathy resembling chronic inflammatory demyelinating polyneuropathy, treatment with IV immunoglobulin (IVG) in conventional doses should be considered. When IVG is unavailable or poorly tolerated, plasma exchange should be considered as an alternative. Unfortunately, few therapeutic studies exist on these rare presentations of SLE.

Seizures are common sequelae of SLE and may result from acute or chronic disease. Acute electrolyte disturbance, response to high-dose steroids, or other acute disturbance may only require temporary anticonvulsant treatment, while more chronic epileptogenic foci may require lifetime prophylaxis. Anticonvulsants may be used in a conventional fashion, emphasizing medications most effective for focal onset or secondarily generalized seizures. Phenytoin and other agents associated with drug-induced lupus are unlikely to actually increase disease activity in SLE, but with chronic use may cause diagnostic confusion for physicians.[1,4]

Treatment of Various Manifestations of Neuropsychiatric SLE [1]

Neuropsychiatric Manifestations	Symptomatic treatment*	Immune-modulating treatment
Seizures	Antiepileptic therapy	High-dose corticosteroids or effective treatment of extraneural disease activity
Delirium	No specific symptomatic therapy	Effective treatment of extraneural disease activity
Psychosis	Antipsychotic medications	Effective treatment of extraneural disease activity
Cerebral vasculopathy	Anticoagulation or antiplatelet agents in selected cases	1. High-dose corticosteroids 2. Cytotoxic immunosuppressives 3. Combination of both
Stroke	1. Anticoagulation 2. Antiplatelet agents	Effective treatment of extraneural disease activity
Transverse myelopathy	No specific symptomatic therapy	1. High-dose corticosteroids 2. Cytotoxic immunosuppressives 3. Combination of both
Cognitive dysfunction	No specific symptomatic therapy	Effective treatment of extraneural disease activity
Anxiety and depression	1. Psychotherapy 2. Cognitive-behavior therapy 3. Supportive-type therapy 4. Biofeedback 5. Pain control 6. Antidepressive agents 7. Anxiolytics	Effective treatment of extraneural disease activity
Drug-induced aseptic meningitis	Withdrawal and avoidance of offending drugs	No specific immunomodulating therapy
Headaches	Migraine treatments Antiplatelet agents	Treatment of extraneural disease activity
Movement disorders	Dopamine antagonists	1. High-dose corticosteroids 2. Anticoagulation if related to anti-phospholipid antibodies
Thrombotic thrombocytopenic purpuras	No specific symptomatic therapy	1. High-dose corticosteroids 2. Cytotoxic immunosuppressives 3. Plasmapheresis
Idiopathic pseudotumor cerebri	1. Carbonic anhydrase inhibitors 2. Repeated lumbar punctures 3. Optic nerve decompression	High-dose corticosteroids

* Includes treatment of secondary causes such as drugs, infections, and metabolic problems related to kidney and liver dysfunction, and electrolyte disturbances.

Treatment of the antiphospholipid syndrome remains controversial, with therapy based predominantly on anecdotal experience. Although many authorities recommend full anticoagulation with warfarin (Coumadin) (although there is no randomized clinical trial to prove this), other authorities support antiplatelet therapy initially, with stronger measures reserved for repeated stroke, progressive myelopathy, or other clear-cut, clinical treatment failure.[4] It is clear that aiming for an INR of 2.0–3.0 is as good as at reducing the risk of

further events than more intensive anticoagulation. This could be done possibly in conjunction with immunosuppressant therapy to suppress production of the antibody.

Cerebral lupus, like the neurological vasculitides, is best managed jointly by neurologists, clinical immunologists, renal physicians, rheumatologists and the primary physicians.[1,4]

Prognosis

- Overall, prognosis for SLE patients has improved dramatically in recent decades, with 70% now living 10 years after diagnosis.[4]
- Neurologic complications worsen prognosis, especially in the presence of refractory seizures, encephalopathy, or paralysis from stroke or myelopathy.
- CNS-specific statistics are not available.
- Active SLE prior to pregnancy is associated with a less favorable maternal and fetal outcome. Hypertension increased the risk of fetal loss and adverse outcome. Phadungkiatwattana et al reported that preeclampsia was the most common maternal complication (20.6%) [36]

MATERIALS AND METHODS

Design of the Study : Cross-sectional and observational study

Study Centre : Institute of Neurology, Madras Medical College and Government General Hospital, Chennai-3.

Study Period : January 2009 to April 2010

Material and selection of subjects:

Consecutive patients who got admitted in Department of Rheumatology or in medical/speciality wards who fit into the ACR criteria for SLE

Exclusion criteria

1. Children below 12 years of age
2. Patients with other comorbid conditions like diabetes, hyperlipidemia, overlap syndromes, cardiac diseases, previous neurologic diseases not related to SLE.
3. Patients who do not satisfy the 1997 Revised Criteria[13] for the Classification of Systemic Lupus Erythematosus (SLE)

STUDY PROCEDURE:

Ethical Consideration:

The study was commenced after obtaining approval from the Institutional Ethical Committee. Patients who were admitted in the Rheumatology, medical or speciality wards were included in the study. Written informed consent was obtained from those who were willing to participate in the study in the prescribed format in the regional language. Left thumb impression was obtained from those patients who are illiterate.

SCREENING:

Apart from age and sex, detailed medical history including mode of onset, duration of illness, constitutional, musculoskeletal, mucocutaneous, renal, cardiac, respiratory symptoms were obtained apart from neurological symptoms. Symptoms pertaining to the central or peripheral nervous system involvement like headache, seizures, altered sensorium, behavioural disturbances, cranial nerve disturbances, motor disturbances, sensory disturbances, autonomic disturbances, involuntary movements, psychiatric symptoms were obtained in detail from the patient or their attenders. Previous records were verified and data collected.

Detailed general examination and neurological examination were performed in all patients. Cognitive involvement could not be studied in detail

in these patients because of technical reasons. Cognitive assessment requires neuropsychological assessment. This is time consuming (1-4 h as recommended by ACR) and needs wholehearted co-operation, which was not readily forthcoming in this cohort of sick patients.[6] Presence of aphasia, psychosis etc also interfered with assessment. Earlier series, which were hospital based did not give much importance to cognitive impairment.[6,8] Mini Mental State Examination(MMSE) scores were obtained in all conscious patients.

Neuropsychiatric syndromes were classified as defined by the ACR.[50] Medical reports were analyzed and NP syndromes diagnosed earlier were also included. Even though the ACR classification lists out the investigations required to make the diagnosis of each NPSLE syndrome, only those investigations, which were of prime importance to make a diagnosis were done.

Serology:

Anti Nuclear Antibody(ANA) testing was obtained from all patients. Anti body to Double stranded DNA(Anti-dsDNA) was obtaines from selected patients. Cut- off value for ANA:

ANA result	Interpretation
<10.0	Negative
≥10.0	Positive

Cut off value for Anti-ds DNA

Value (IU/mL)	Interpretation
<30	Negative
30 – 75	Borderline Positive
>75	Positive

Imaging:

Atleast one imaging of either CT Brain or MRI or both was done on all patients who were suspected to have CNS lupus.

Nerve Conduction Studies:

Routine Nerve conduction studies(NCS) were done in all patients. The studies included motor and sensory conduction of bilateral ulnar, median, tibial and peroneal nerves including latency, amplitude, conduction velocity and F wave latencies. NCS of selected nerves and Electromyography(EMG) was done in selected patients who had abnormal routine nerve conduction studies. EMG was also done for patients who had features of myopathy.

Nerve Biopsy:

Nerve Biopsy of Sural Nerve was done only in two patients who had abnormal nerve conduction. Some patients did not consent for a nerve biopsy.

The biopsy specimen were sent to Department of Neuropathology at NIMHANS, Bangalore for Histopathological evaluation.

EEG:

Routine EEG was done in patients who were suspected to have seizures. A EEG study consisted of awake EEG with activation procedures which included sleep deprivation, sleep record of 20 minutes, hyperventilation and photic responses(upto 24Hz). The seizure patients were classified based on clinical semiology and EEG patterns.

CSF analysis:

CSF analysis for biochemical profiles(protein, sugar), gram stain and cell count were done in selected cases. The primary aim was to exclude a infection or a primary demyelination.

DSM IV criteria was applied to categorize patients who had features of psychosis and anxiety.

To analyse the patients for features of depression, Hamilton Rating Scale (HAM 21) questionnaire was employed in all patients and the patients were categoried as mild, moderate or severe depression.

Hamilton Rating Scale for Depression (HAM 21)

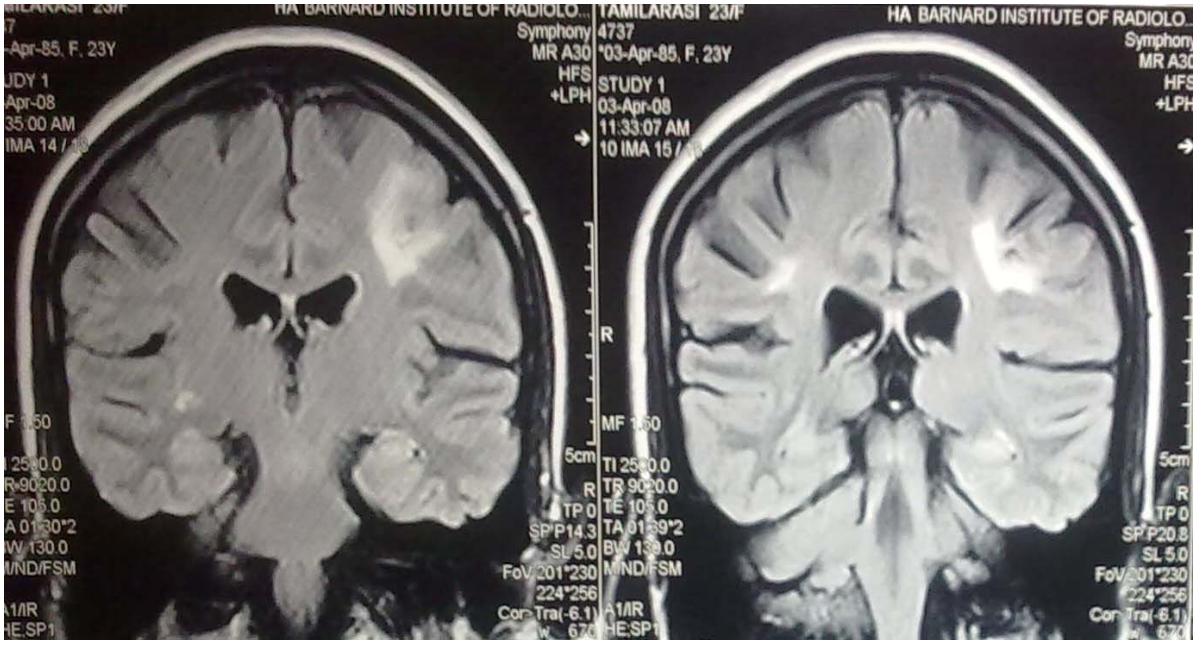
A 21 point questionnaire(see Annexure II) was employed and all the patients were assessed for the presence or absence of depression and interpreted based on the scores obtained as shown below:

SCORE	INTERPRETATION
0 to 6	Normal
7 to 17	Mild Depression
18 to 24	Moderate Depression
>24	Severe Depression

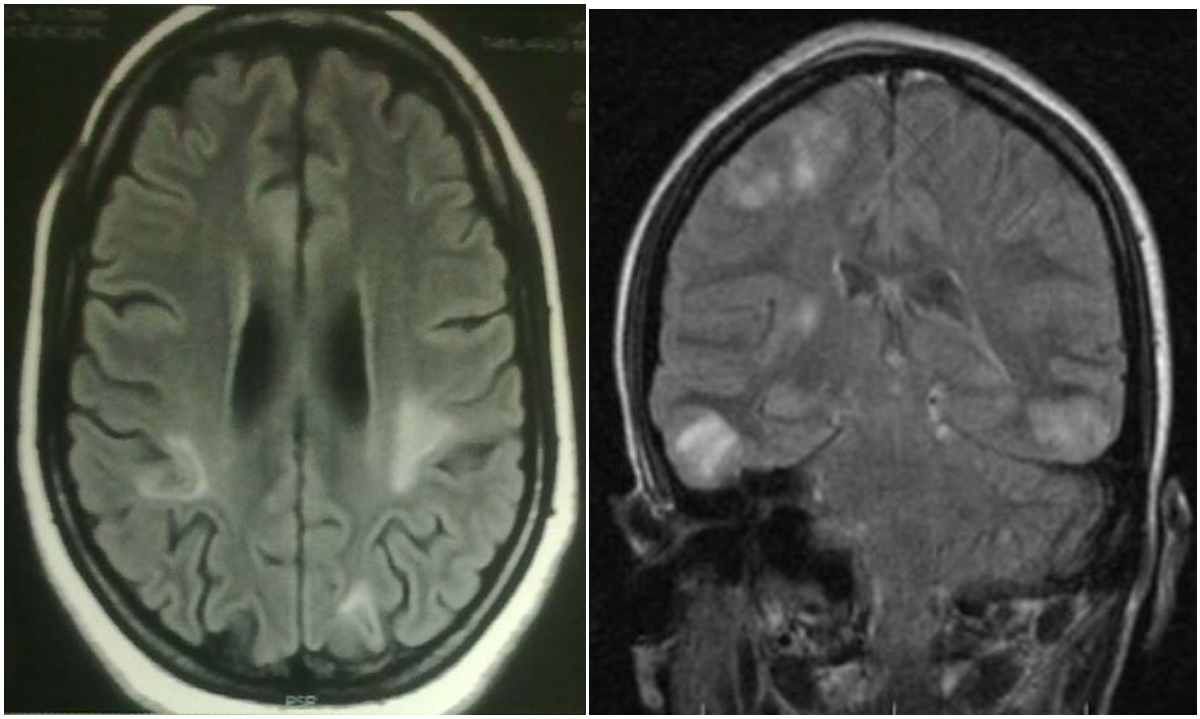
Statistical Analysis:

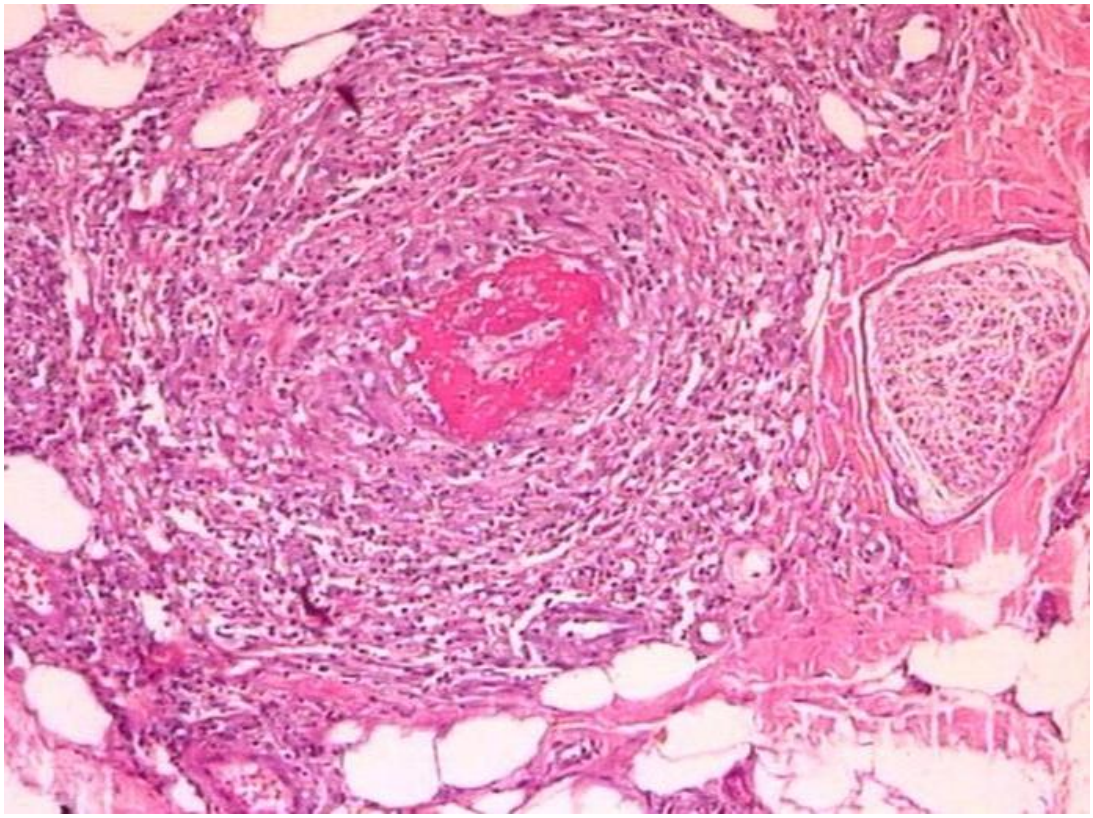
The statistical analysis was performed using SPSS software, version 17.0. Results are presented as the mean ± S.D., except for frequencies, which are expressed as percentages. Comparison between groups were made by means of Chi square test used when appropriate. P values less than 0.05 were considered significant. Graphs were produced using Microsoft Excel.

Patients showing skin rashes and hair loss

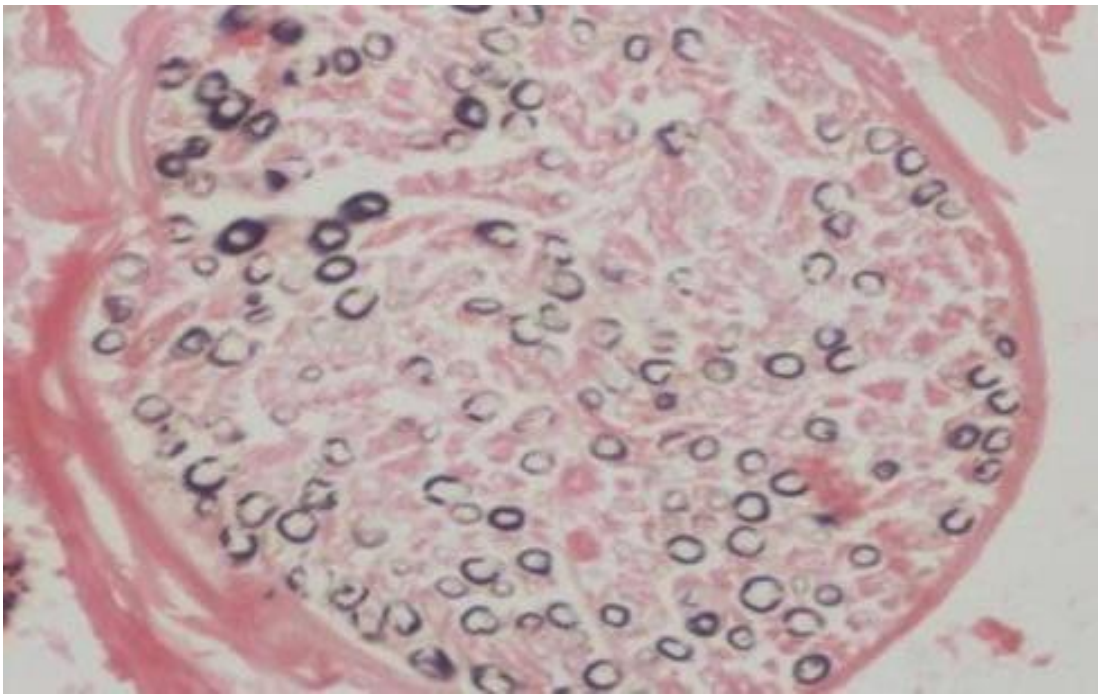


MRI – FLAIR sequences showing multiple hyperintense lesions





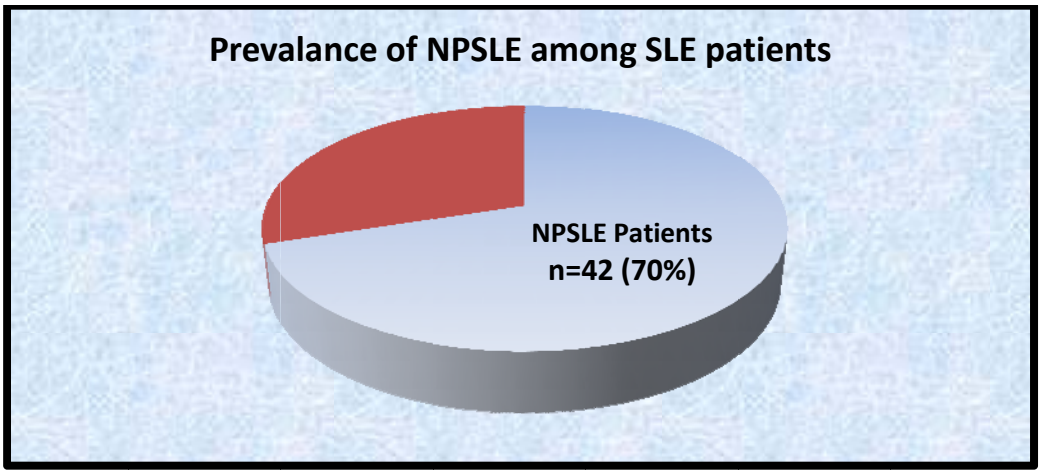
HPE- H&E stain showing inflammation around the vessels



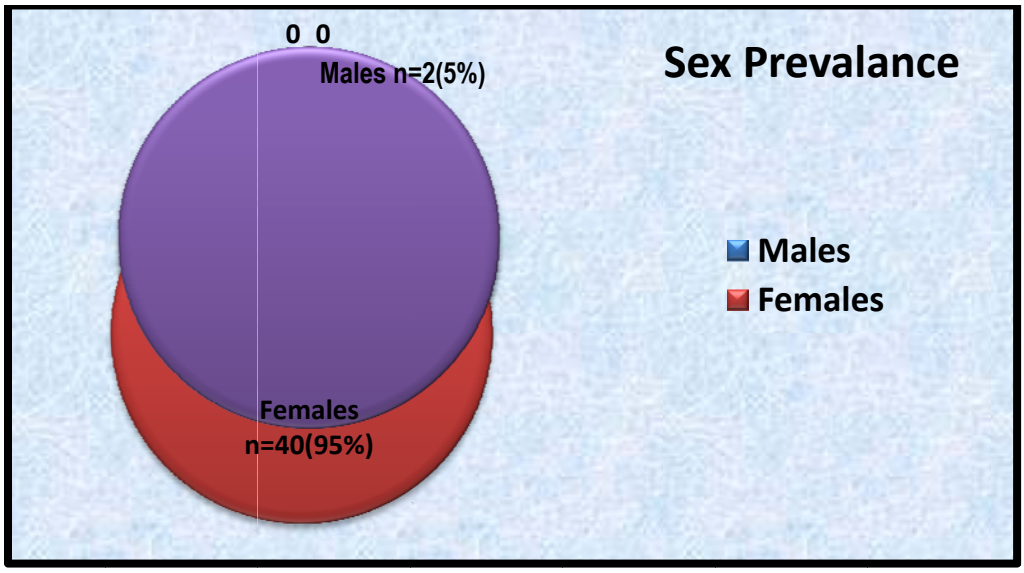
K-Pal Stain for myelin showing loss of myelin

RESULTS AND OBSERVATIONS

A total of contiguous 60 patients diagnosed to have definite SLE based on ACR criteria(atleast four out of eleven criteria) were included in the study. Among these patients, 42 patients had atleast one feature of Neuropsychiatric manifestations (NPSLE) who were studied in detail. Prevalance of NPSLE among SLE patients = 70% (n = 42 out of 60)



Sex: Out of 42, 40(95%) were females and 2(5%) were males

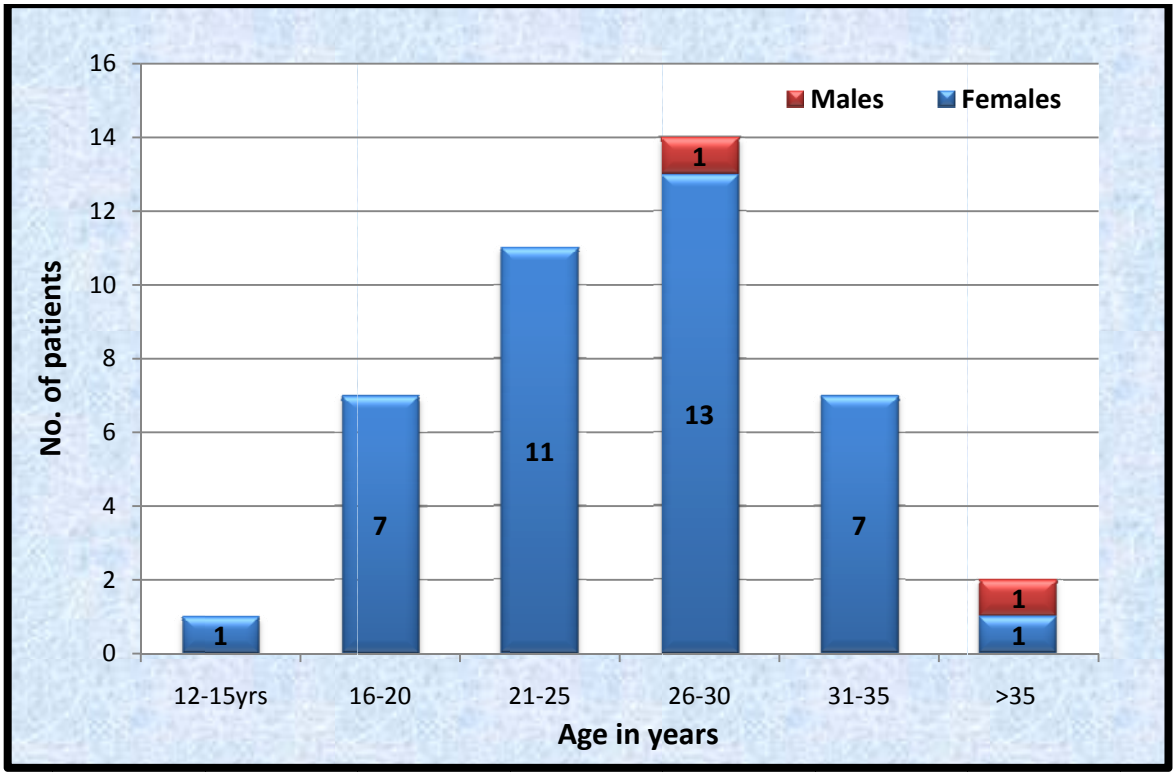


Age:

The age range was between 13 and 41 years. The distribution of age was as follows:

Age (years)	Females	Males	Total
12-15	1	0	**1**
16-20	7	0	**7**
21-25	11	0	**11**
26-30	13	1	**14**
31-35	7	0	**7**
>35	1	1	**2**
Total	**40**	**2**	**42**

The mean age of the studied patients was 25.9 years(SD:2.6). The median was 26 years.

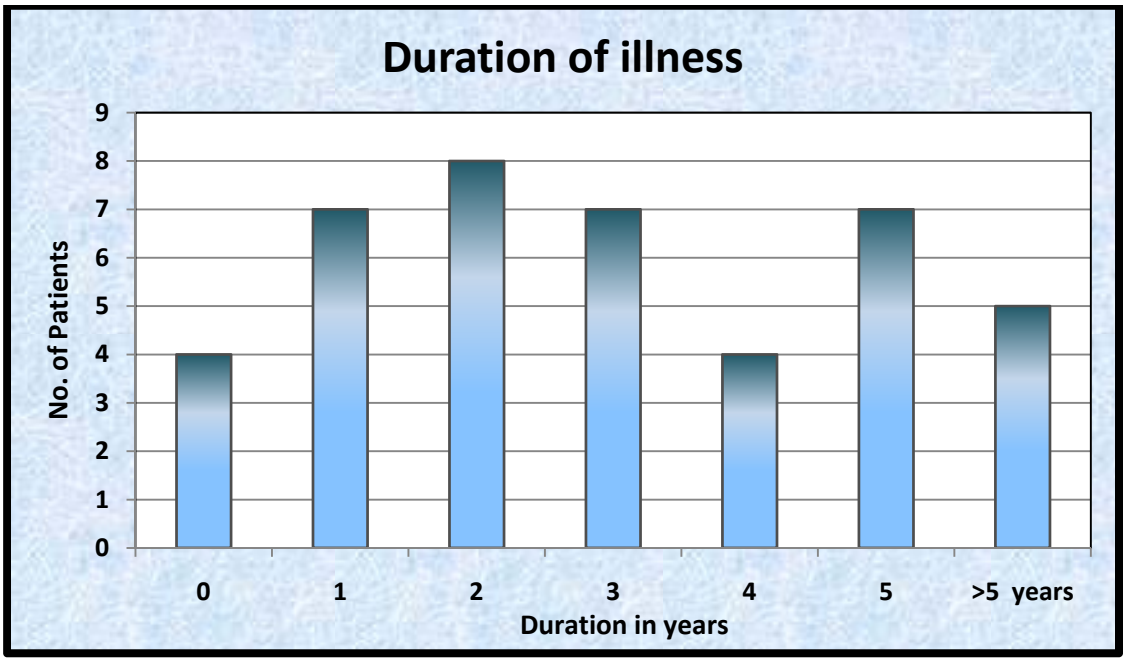


Age Distribution

Duration of Illness:

Four patients(9.5%) presented with neurologic symptoms as the first manifestations of the illness. The maximum duration was 11 years. The mean duration was 3.16 years. Median was 3. The mode was 2 years. The distribution of duration of illness of SLE in the studied patients is as follows:

Duration (years)	No of patients	Percentage n=42(100%)
0	4	9.5%
1	7	16.6%
2	8	19%
3	7	16.6%
4	4	9.5%
5	7	16.6%
>5yrs	5	12%
TOTAL	**42**	**100%**



ACR criteria of SLE during presentation:

Though 4 out of the 11 of the revised ACR criteria has to be fulfilled for entry into the study many patients fulfilled even more than 4 criteria. The distribution is as follows:

ACR criteria (out of 11)	No of patients (Total n=42)	Percentage
4	30	71.4%
5	7	16.6%
6	3	7.2%
≥7	2	4.8%

Skin manifestations was the commonest association seen in 71.4%(n=30) of patients followed by nephritis in 33.3%(n=14) among those who had atleast one NPSLE manifestation.

Serology:

ANA was positive in all the patients(100% positivity, n=42). Anti dsDNA was positive in 20 patients among 32 patients who did the testing.(62.5% positivity)

Imaging:

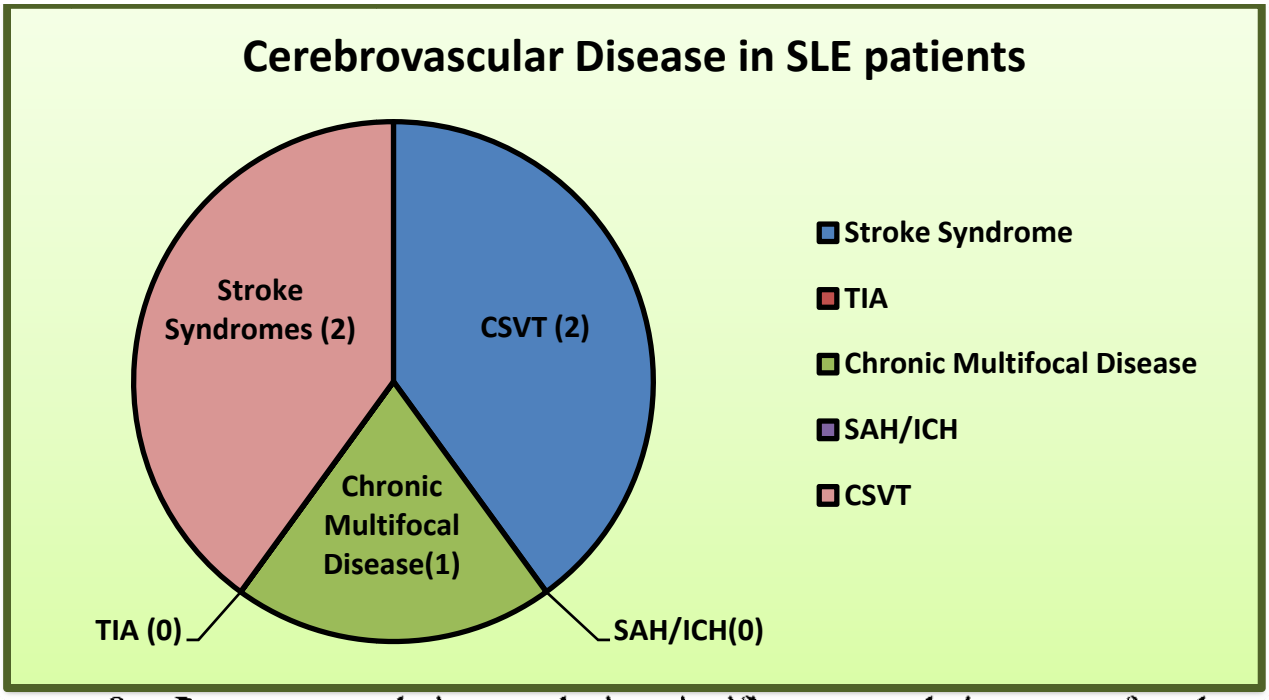
Of the 42 patients, 30(71%) patients had done CT scan of brain, 8(19%) patients did MRI and four(10%) did both CT and MRI brain. An abnormal imaging had a significant correlation with CVA (P <0.0001) and a normal imaging has significant correlation with psychosis (P <0.0001).

NEUROPSYCHIATRIC MANIFESTATIONS: (NPSLE)

NPSLE SYNDROMES	No of patients	Percentage
CENTRAL NERVOUS SYSTEM		
1. Aseptic meningitis	-	0%
2. Cerebrovascular disease	5	12%
3. Demyelinating syndrome	-	0%
4. Headache	23	54.7%
5. Movement disorder	2	4.8%
6. Myelopathy	-	0%
7. Seizure disorders	14	33.3%
8. Acute confusional state	7	16.6%
9. Anxiety disorder	-	0%
10. Mood disorder(Depression)	20	47.6%
11. Psychosis	5	12%
PERIPHERAL NERVOUS SYSTEM		
1. Acute inflammatory demyelinating polyradiculo-neuropathy(AIDP)	1	2.4%
2. Autonomic disorder	-	0%
3. Mononeuropathy, single/multiplex	3	7.2%
4. Myasthenia gravis	-	0%
5. Neuropathy, cranial	-	0%
6. Polyneuropathy	1	2.4%
7. Plexopathy	-	0%
8. Myositis/myopathy	6	14%

CEREBROVASCULAR DISEASE:

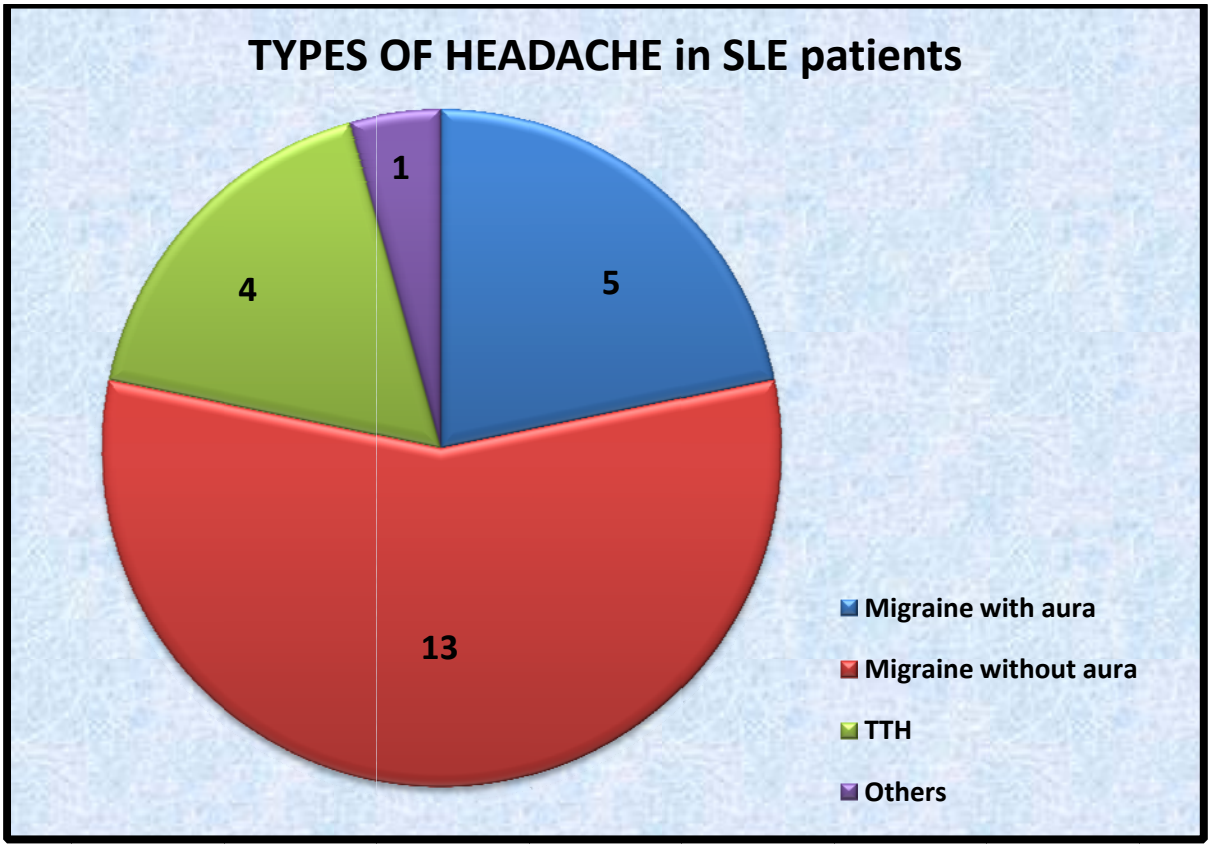
Type of CVA	No of patients	Percentage
Stroke syndrome	2	40%
TIA	0	0%
Chronic Multifocal Disease	1	20%
SAH/ICH	0	0%
Cortical Sinus Venous Thrombosis	2	40%
TOTAL	**5**	**100%**



On Pearson correlation analysis, significant correlation was found between cerebrovascular accident (CVA) and acute confusional state ($P = 0.01$). No correlation was found with age.

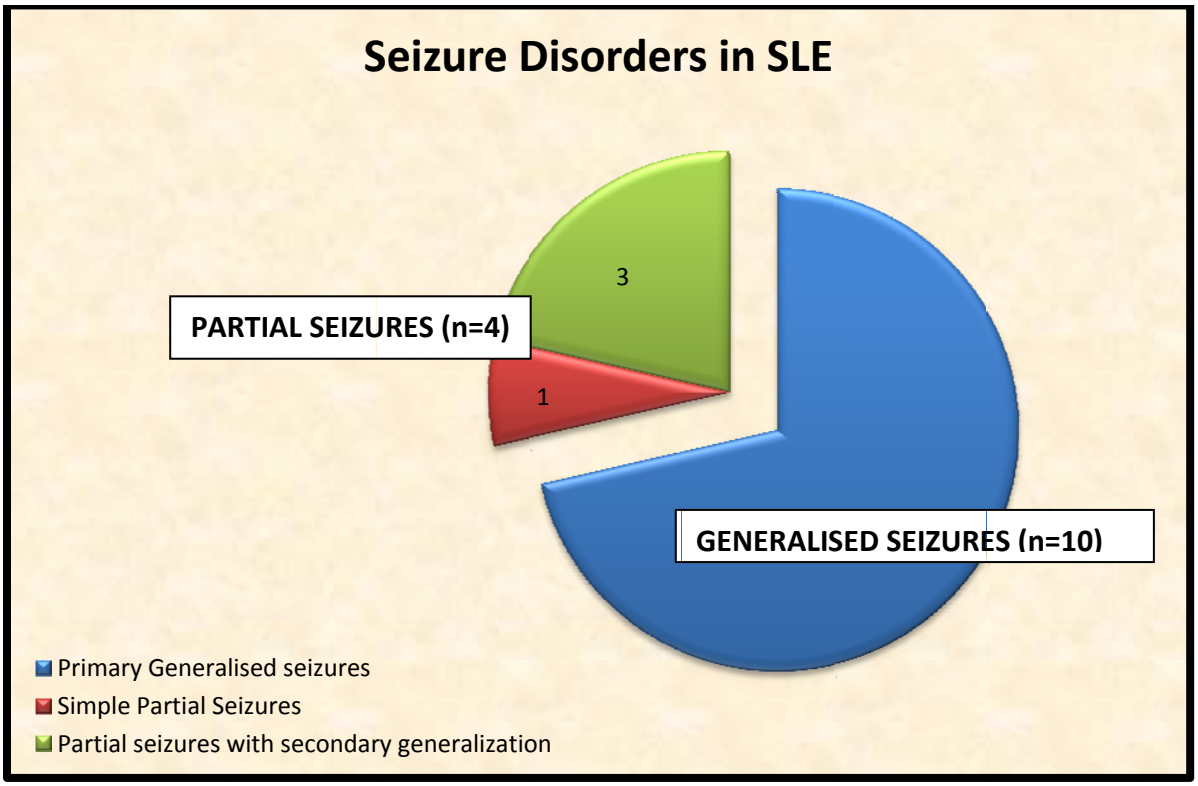
Headache:

TYPES OF HEADACHE	No. of Patients	Percentage
Migraine with Aura	5	21.7%
Migraine without Aura	13	56.5%
Tension type Headache	4	17.3%
Cluster Headache	-	0%
Others	1	4.3%
TOTAL	**23**	**100%**



SEIZURES AND SEIZURE DISORDERS:

SEIZURE TYPE		No of Patients		Percentage	
Primary generalized seizures	Tonic clonic or tonic or clonic	10	10	71.4%	71.4%
	Atonic or astatic seizures	-		0%	
	Absence seizures	-		0%	
	Myoclonic seizures	-		0%	
Partial or focal seizures	Simple	1	4	7.1%	28.5%
	Complex	-		0%	
	Simple or Complex with secondary generalisation	3		21.4%	
TOTAL		**14**		**100%**	



PERIPHERAL NERVE DISORDERS:

- AIDP was noted in one patient(2.4%)
- Polyneuropathy was noted in one patient(2.4%) whose sural nerve biopsy showed axonal changes in histopathology.
- Carpal Tunnel Syndrome was seen in two patients(4.8%)
- Mononeuritis Multiplex involving bilateral ulnar and right tibial nerves was seen in one patient(2.4%)

MOOD DISORDERS:

20 patients(47.6%) had mood disorders, all of whom had features of major depression. None had features of mania or mixed mood disorders. The Hamilton rating Scale for Depression was used to categorize depression into mild moderate and severe and those who had moderate or severe depression were considered to have major depressive episode.

Hamilton Rating Scale for Depression (HAM 21)

SCORE	INTERPRETATION	No. of Patients	Percentage
0 to 6	**Normal**	13	31%
7 to 17	**Mild Depression**	9	21.4%
18 to 24	**Moderate Depression**	11	26.2%
>24	**Severe Depression**	9	21.4%
TOTAL		42	100%

MOVEMENT DISORDERS:

Two patients (4.8%) had tremors of both hands, symmetrical, predominantly action induced (distal >proximal). No chorea was noted in the studied patients.

TREATMENT:

All patients were treated with steroids initially. Methylprednisolone was instituted in some of them while others received oral steroids(Prednisolone). The dose of Methyprednisolone was 1 gram per day for five days followed by oral steroids. The dose of oral prednisolone was 1mg/kg body weight.

Eight(19%) of the chronic patients especially those with associated lupus nephritis and the patient with polyneuropathy were started on Cycophosphamide at a dose of 500 to 750 mg/m^2 in divided doses for 3 days every month. Methotrexate and Hydroxychloroquine were also initiated in some patients. Disease specific treatments were instituted for the NPSLE syndromes (viz. antiepileptics, antiplatelets, anticoagulants, NSAIDs, antidepressants, antipsychotics)

No mortality was noted till discharge. The cerebrovascular disease patients and polyneuropathy patient had severe morbidity on discharge. The patients who presented with seizure disorder, headache, psychosis, mood disorders had significant improvement on discharge.

DISCUSSION

The prevalence of rigorously defined neuropsychiatric manifestations was high at study entry in our cohort as 70% of our patients had one or more NPSLE syndromes. 9.5% (n=4) of patients presented with NPSLE as the first manifestation of SLE. The study describes Neuropsychiatric syndromes significant enough to warrant hospitalization as well NPSLE syndromes occurring in SLE patients who are significantly morbid from other systemic illness.

The prevalence of specific NPSLE syndromes varies widely in the literature. Though community based studies were available for comparison, hospital based studies are very few and one such study was conducted in India by Robert et.al. from Trivandrum.[6] The other study is the San Antonio Lupus Study of Neuropsychiatric Disease (SALUD), by Brey et.al.[7] These two studies were compared with the present study and the prevalence of the NPSLE syndromes were compared with the available data.

The prevalence of the NPSLE among the admitted SLE patients was 70% in the present study. This was 78% in Robert et.al.[6] (Kerala) study and 80% in SALUD study (Brey et.al.).[7] The prevalence was almost comparable to the available data.

The female to male sex ratio was 20:1 in the present study. The females were 100% in Robert et.al[6] study whereas it was 15:1 in SALUD study.[7]

The commonest NPSLE syndrome seen in this study was Headache in 54.7% (n=23). This feature was in concordance with the other studies which also reported headache as the commonest presentation of NPSLE syndromes. The prevalence was 55.6% in Robert et.al.[6] study and 57% in SALUD study. The most common form of headache was migraine without aura seen in 56.5% patients in contrast to SALUD study where migraine with aura was the commonest headache seen in 42%.[7]

The next most common presentation was Mood disorders noted in 47.6% (n=20) patients as compared to 51% in SALUD study.[7] But mood disorder was not seen in Robert et.al. series.

Routine nerve conduction study done in all patients could detect mononeuropathies, especially carpal tunnel syndrome in two patients(4.8%). One patient(2.4%) had mononeuritis multiplex like presentation of bilateral ulnar, and right tibial nerves. The cumulative involvement of peripheral nerve in this study by electrophysiology is 12%(n=5).

Cognitive involvement could not be studied in detail in these patients because of technical reasons. Cognitive assessment requires neuropsychological assessment. This is time consuming (1-4 h as recommended by ACR) and needs

wholehearted co-operation, which was not readily forthcoming in this cohort of sick patients. Presence of aphasia, psychosis etc also interfered with assessment. Earlier series, which were hospital based did not give much importance to cognitive impairment.

An interesting and new finding was the tremor disorder seen in 2 (4.8%) of the patients. This syndrome has not been defined in the ACR nomenclature and rare in literature.[51] Both the patients had bilateral distal fine tremor, prominent during posture and action. This type of tremor can occur in essential tremor syndrome or as part of enhanced physiologic tremor, due to drugs or fatigue. Drug induced tremor could not be ruled out in any patients. It is likely that some or all of these factors were responsible for tremor in our patients either causally or as a contributory factor. The available imaging did not show any focal abnormalities. It is likely that this sign was not detected in many patients as index of suspicion was low and it did not often produce any symptoms.

Cerebrovascular disease was seen in 12% of patients(n=5). Of these, 40% (n=2) was Cortical Sinus Venous Thrombosis(CSVT) and 40% (n=2) was stroke syndromes. Robert et.al.[6] from kerala reported that cerebrovascular disease occurred in 16.2% of patients.

NPSLE SYNDROMES **CENTRAL NERVOUS SYSTEM**	**The present study** n=42 (100%)	**Robert.et.al.[6] (Kerala)** n=39(100%)	**Brey. et.al.[7] SALUD study** n=128 (100%)
1. Aseptic meningitis	NS	NS	NS
2. Cerebrovascular disease	**5 (12%)**	**6(16.2%)**	**2 (2%)**
3. Demyelinating syndrome	NS	NS	NS
4. Headache	**23 (54.7%)**	**20 (55.6%)**	**73 (57%)**
Migraine with Aura	5 (21.7%)	10 (50%)	31 (42%)
Migraine without Aura	13 (56.5%)		20 (27%)
Tension type Headache	4 (17.3%)	10 (50%)	21 (29%)
Others	1 (4.3%)	NS	1 (1%)
5. Movement disorder	**2 (4.8%)**	**9 (23.1%)**	**1 (1%)**
6. Myelopathy	NS	NS	NS
7. Seizure disorders	**14 (33.3%)**	**8 (20.5%)**	**21 (16%)**
Partial seizures	1 (7.1%)		21(100%)
Primary Generalised	10 (71.4%)		NS
Secondary Generalised	3 (21.4%)		NS
8. Acute confusional state	**7 (16.6%)**	**6(16.2%)**	**NS**
9. Anxiety disorder	NS	NS	**27 (24%)**
10.Mood disorder(Depression)	**20 (47.6%)**	NS	**62 (51%)**
11.Psychosis	**5 (12%)**	**6(16.2%)**	**6 (5%)**

NPSLE SYNDROMES **PERIPHERAL NERVOUS SYSTEM**	**The present study** n=42 (100%)	**Robert.et.al.**[6] **(Kerala)** n=39(100%)	**Brey. et.al.**[7] **SALUD study** n=128 (100%)
1. Acute inflammatory demyelinating polyradiculo-neuropathy(AIDP)	**1 (2.4%)**	NS	NS
2. Autonomic disorder	NS	NS	NS
3. Mononeuropathy, single/multiplex	**3 (7.2%)**	**3 (7.9%)**	**9 (8%)**
4. Myasthenia gravis	NS	NS	NS
5. Neuropathy, cranial	NS	NS	**2 (2%)**
6. Polyneuropathy	**1 (2.4%)**	NS	**22 (20%)**
7. Plexopathy	NS	NS	NS
8. Myositis/myopathy*	**6 (14%)**	**1 (2.56%)**	**-**

NS – Not Seen in the study, * not defined in ACR nomenclature

Some of the defined NPSLE syndromes like demyelinating disease, aseptic meningitis, myelopathy, anxiety disorder, autonomic disorder, myasthenia, cranial neuropathy and plexopathy were not seen in the present study.

The presence of past or current psychiatric diagnoses based on DSM-IV criteria is also common in the present cohort, although past or current psychosis is rare. The frequency of individual psychiatric manifestations is comparable to that previously reported.[6,7,8]

The main weakness of the study is the small sample size, and therefore the results should to be interpreted with caution. As a cross-sectional study, the validity of disease history depends on the documentation of past disease episodes. Though this is unlikely to have a substantial effect on the prevalence rates of the NP syndromes, reliable discrimination between primary NPSLE, secondary NPSLE, and concurrent disease process becomes problematic. It has been estimated that two-thirds of NP manifestations in SLE are not directly related to NPSLE but are due to secondary causes such as drugs, infections, and metabolic complications of the disease.[52,53] Prospective analyses would help in discriminating between primary and secondary NPSLE.

CONCLUSIONS

1. Atleast one Neuropsychiatric SLE (NPSLE) syndrome was found in 70% of SLE patients admitted.
2. Females were more predominant (F:M=20:1)
3. 9.5% of patients presented with NPSLE as the first manifestation of SLE.
4. Headache was the most common presentation seen in 54.7% patients followed by mood disorders(depression) (47.6%). Migraine without aura was the most common type of headache noted.
5. Psychosis was seen only in 12% of patients.
6. Peripheral nerve disorders were seen in 12% of the patients.
7. Seizure disorder was seen in 33% of patients, generalized seizure being the most common among them.
8. Tremor disorder seen in 4.8% of the patients.
9. Some of the defined NPSLE syndromes like demyelinating diseases, aseptic meningitis, myelopathy, anxiety disorder, autonomic disorder, myasthenia, cranial neuropathy and plexopathy were not observed in the present study.

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ANNEXURE 1

Case Definitions for Neuropsychiatric Syndromes in Systemic Lupus Erythematosus

(ACR Ad Hoc committee on neuropsychiatric lupus nomenclature: The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608, and from John Wiley and Sons.)

1. **Acute confusional state**

Disturbance of consciousness or level of arousal characterized by reduced ability to focus, maintain, or shift attention, and accompanied by disturbances of cognition, mood, affect, and/or behavior. The disturbances typically develop over hours to days and tend to fluctuate during the course of the day. They include hypo- and hyperaroused states and encompass the spectrum from delirium to coma.

Diagnostic criteria:

Disturbance of consciousness or level of arousal with reduced ability to focus, maintain, or shift attention, and one or more of the following developing over a short period of time (hours to days) and tending to fluctuate during the course of the day:

a. Acute or subacute change in cognition that may include memory deficit and disorientation.

b. A change in behavior, mood, or affect (e.g., restlessness, overactivity, reversal of the sleep/wakefulness cycle, irritability, apathy, anxiety, mood lability, etc.).

Exclusions:

• Primary mental/neurological disorder not related to systemic lupus erythematosus **(**SLE).
• Metabolic disturbances (including glucose, electrolytes, fluid, osmolarity).
• Substance or drug-induced delirium (including withdrawal).
• Cerebral infections.

Associations:

• Marked psychosocial stress.
• Corticosteroid use.
• Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

2. **Acute inflammatory demyelinating polyradiculoneuropathy**

Diagnostic criteria:

a. Clinical features

i. Progressive polyradiculoneuropathy, usually ascending and predominantly motor, which peaks usually within 21 days or less.

ii. Reflex loss.

iii. Symmetric, may involve the trunk and may cause respiratory failure.

b. Cerebrospinal fluid(CSF)

i. Increased CSF protein without pleocytosis.

c. Supportive evidence by nerve conduction study including F-wave ascertainment whereby there is one abnormality in three nerves.The abnormalities are:

i. Conduction block in which the amplitude of compound muscle action potential diminishes with more proximal sites of nerve stimulation.

ii. F waves may be absent or prolonged.

iii. Slowing of conduction velocity.

iv. Prolongation of distal latencies.

Exclusions:

• Acute spinal cord disease.
• Botulism.

• Poliomyelitis and other infections.
• Acute myasthenia gravis.

3. **Anxiety disorder**
Anticipation of danger or misfortune accompanied by apprehension, dysphoria, or tension. Includes generalized anxiety, panic disorder, panic attacks, and obsessive-compulsive disorders.
Diagnostic criteria:
Both of the following:
a. Prominent anxiety, panic disorder, panic attacks, or obsessions or compulsions.
b. Disturbance causes clinically significant distress or impaired social, occupational, or other important functioning.
Exclusions:
• Adjustment disorder with anxiety (e.g., maladaptive response to stress of having SLE).
• Substance- or drug-induced anxiety.
• Anxiety occurring exclusively during the course of an acute confusional state, a mood disorder, or psychosis.

Associations:
• Metabolic disorders, e.g., hyperthyroidism, pheochromocytoma.
• Marked psychosocial stress.
• Corticosteroid use.

4. **Aseptic Meningitis**
Diagnostic criteria:
All the following:
a. Acute or subacute onset of headache with photophobia, neck stiffness, and fever.
b. Signs of meningeal irritation.
c. Abnormal CSF.
Exclusions:
Central nervous system (CNS) or meningeal inflammation because of:
a. Infection by bacteria, mycobacteria, viruses, fungi, parasites.
b. Subarachnoid hemorrhage.
c. Malignancy (leukemia, lymphoma, or carcinoma) or granulomatous disease (sarcoidosis).
d. Medications: nonsteroidal anti-inflammatory drugs, intravenous immunoglobulin, azathioprine, etc.

5. **Autonomic disorder**
Disorder of the autonomic nervous system with orthostatic hypotension, sphincteric erectile/ejaculatory dysfunction, anhidrosis, heat intolerance, constipation.
Diagnostic criteria:
Symptoms and abnormal response to provocative tests:
Test normal range
a. Blood pressure response to standing: fall in blood pressure more than 30/15 mmHg or vertical tilt (systolic/diastolic).
b. Heart rate response to standing: increases 11–29 beats/minute.
c. Heart rate variation with respiration: maximum–minimum heart rate: 15 beats/minute; E:I ratio (ratio of heart rate during expiration and inspiration): 1:2.
c. Valsalva ratio: 1:4.
d. Sweat test: Sweating over all body and limbs.
Exclusions:
• Autonomic dysfunction with Lambert-Eaton syndrome.
• Medications: tricyclic antidepressants.

• Poisons: organophosphates.
• Shy-Drager syndrome.

Associations:

• Diabetic neuropathy and peripheral neuropathy of other causes.
• Autonomic failure in elderly.

6. **Cerebrovascular disease**

Diagnostic criteria:

One of the following and supporting radioimaging study:

a. Stroke syndrome: acute focal neurological deficit persisting more than 24 hours (or lasting less than 24 hours with computed tomography (CT) or magnetic resonance imaging (MRI) abnormality consistent with physical findings/symptoms.

b. Transient ischemic attack: acute, focal neurological deficit with clinical resolution within 24 hours (without corresponding lesion on CT or MRI).

c. Chronic multifocal disease: recurrent or progressive neurological deterioration attributable to cerebrovascular disease.

d. Subarachnoid and intracranial hemorrhage: bleeding documented by CSF findings, MRI/CT.

e. Sinus thrombosis: Acute, focal neurological deficit in the presence of increased intracranial pressure.

Note: The finding of unidentified bright objects on MRI without clinical manifestations is not classified at the present time.

Exclusions:

• Infection with space occupying lesions in the brain.
• Intracranial tumor.
• Trauma.
• Vascular malformation.
• Hypoglycemia.

Associations:

• Diabetes mellitus.
• Dyslipidemia.
• Atherosclerotic vascular disease.
• Atrial fibrillation.
• Valvular heart disease.
• Atrial septal defect.
• Hypercoagulability state.
• Antiphospholipid antibody syndrome.
• Hypertension.
• Smoking.
• Cocaine or amphetamine abuse.

7. **Cognitive Dysfunction**

Significant deficits in any or all of the following cognitive functions: simple or complex attention, reasoning, executive skills (e.g., planning, organizing, sequencing), memory (e.g., learning and recall), visuospatial processing, language (e.g., verbal fluency), and psychomotor speed. Cognitive dysfunction implies a decline from a higher level of functioning and ranges from mild impairment to severe dementia. It may or may not impede social, educational, or occupational functioning, depending on the function(s) impaired and the severity of impairment. Subjective complaints of cognitive dysfunction are common and may not be objectively verifiable. Neuropsychological testing should be done in suspected cognitive dysfunction, and its interpretation should be done with a neuropsychologist.

Diagnostic criteria:

a. Documented impairment in one or more of the following cognitive domains:
i. Simple attention.
ii. Complex attention.
iii. Memory (e.g., learning and recall).
iv. Visuospatial processing.
v. Language (e.g., verbal fluency).
vi. Reasoning/problem solving.
vii. Psychomotor speed.
viii. Executive functions (e.g., planning, organizing, and sequencing).
b. The cognitive deficits represent a significant decline from a former level of functioning (if known).
c. The cognitive deficits may cause varying degrees of impairment in social, educational, or occupational functioning, depending on the function(s) impaired and the degree of impairment.

Associations:

• Substance abuse.
• Medication (steroids, sedatives).
• History of learning disabilities.
• History of head injury.
• Other primary neurological and psychiatric disorders.
• Metabolic disturbances, particularly uremia and diabetes.
• Antiphospholipid antibody syndrome.
• Coexisting emotional distress, fatigue, and pain.

8. **Demyelinating syndrome**

Diagnostic criteria:

Two or more of the following, each occurring at different times, or one of the following occurring on at least two different occasions:
a. Multiple discrete areas of damage to white matter within CNS, causing one or more limbs to become weak with sensory loss.
b. Transverse myelopathy.
c. Optic neuropathy.
d. Diplopia because of isolated nerve palsies or internuclear ophthalmoplegia.
e. Brain stem disease with vertigo, vomiting, ataxia, dysarthria, or dysphagia.
f. Other cranial nerve palsies.

Exclusions:

• Infections, e.g., tuberculosis, human T-cell lymphotropic virus-I, HIV, cytomegalovirus, *Borrelia*, CNS Whipple's disease, progressive multifocal leukoencephalopathy, syphilis.
• Vitamin B12 deficiency.

Associations:

• Structural lesions, e.g., tumor, arteriovenous malformation**.**
• Familial disorders, e.g., hereditary spastic paraplegia, ataxia, and leukodystrophies.
• Sarcoid, Behçet's disease, other vasculitis.
• Multiple sclerosis.

9. **Headache**

a. Migraine
i. Migraine without aura: Idiopathic, recurrent headache manifested by attacks lasting 4–72 hours. Typical characteristics are unilateral location, pulsating quality, moderate-to-severe intensity, aggravation by routine physical activity, and associated with nausea, vomiting, photo- and phonophobia. At least five attacks fulfilling the aforementioned criteria.
ii. Migraine with aura: Idiopathic, recurrent disorder manifested by attacks of neurological symptoms localizable to cerebral cortex or brain stem, usually gradually developing over 5–20 minutes and

lasting less than 60 minutes. Headache, nausea, and/or photophobia usually follow neurologic aura symptoms directly or after an interval of less than 1 hour. Headache usually
lasts 4–72 hours, but may be completely absent.
b. Tension headache (episodic tension-type headache).
Recurrent episodes of headaches lasting minutes to days. Pain typically pressing/tightening in quality, of mild-to-moderate intensity, bilateral in location, and does not worsen with routine physical activity. Nausea is rare, but photophobia and phonophobia may be present. At least 10 previous headaches fulfilling these criteria
c. Cluster headache.
Attacks of severe, strictly unilateral pain, orbital, supraorbital, and/or temporal, usually lasting 15–180 minutes and occurring from at least once every other day up to eight times per day. Associated with one or more of the following: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, eyelid edema. Attacks occur in series for weeks or months ("cluster" periods), separated by remissions of usually months or years.
d. Headache from intracranial hypertension (also called pseudotumor cerebri, benign intracranial hypertension)
All of the following:
i. Increased intracranial pressure (200 mm H2O) measured by lumbar puncture.
ii. Normal neurological findings, except for papilledema and possible nerve VI palsy.
iii. No mass lesion and no ventricular enlargement on neuroimaging.
iv. Normal or low protein and normal white cell count in CSF.
v. No evidence of venous sinus thrombosis.
e. Intractable headache, nonspecific.
Exclusions:
• Aseptic meningitis (including drug-induced).
• Drug-induced pseudotumor cerebri (oral contraceptives, sulfonamides, trimethoprim, etc.).
• CNS infection.
• Tumors and other structural lesions.
• Low intracranial pressure.
• Trauma.
• Metabolic headache that remits with elimination of cause (carbon monoxide exposure).
• Withdrawal (caffeine, etc.).
• Seizure/postictal state.
• Sepsis.
• Intracranial hemorrhage or vascular occlusion.

10. **Mononeuropathy (single/multiplex)**
Disturbed function of one or more peripheral nerve(s) resulting in weakness/paralysis or sensory dysfunction because of either conduction block in motor nerve fibers or axonal loss. Conduction block is related to demyelination with preservation of axon continuity. Remyelination may be rapid and complete. If axonal interruption takes place, axonal degeneration occurs below the site of interruption and recovery is often slow and incomplete. Sensory symptoms and sensory loss may affect all modalities or be restricted to certain forms of sensation.
Diagnostic criteria:
a. Clinical demonstration of motor/sensory disturbances in the distribution of a peripheral nerve *and/or*
b. Abnormalities on nerve conduction studies or electromyogram (EMG) (i.e., concentric needle examination).
Associations:
• Diabetic neuropathy.
• Local damage from mechanical injury, radiation, malignancy, sarcoid.

• Infection: Lyme disease, HIV, herpes.
• Vasculitis, polyarteritis nodosa, Wegener's granulomatosis, cryoglobulinemia, rheumatoid arthritis, Sjögren's syndrome, etc.

11. **Mood disorders**
Prominent and persistent disturbance in mood characterized by:
• Depressed mood or markedly diminished interest or pleasure in almost all activities *or*
• Elevated, expansive or irritable mood.
Diagnostic criteria:
a. Major depressive-like episode.
One or more major depressive episodes with at least five of the following symptoms, including either i or ii or both, during a 2-week period and nearly every day:
i. Depressed mood most of the day, by subjective report or observation made by others.
ii. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, by subjective report or observation made by others.
iii.
(1) Significant weight loss without dieting or weight gain (>5% of body weight in 1 month).
(2) Insomnia or hypersomnia. Psychomotor agitation or retardation (observable by others, not merely subjective feeling of restlessness or being slowed down).
(3) Fatigue or loss of energy.
(4) Feelings of worthlessness or excessive or inappropriate guilt (may be delusional).
(5) Diminished ability to think or concentrate, or indecisiveness.
(6) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
b. Mood disorder with depressive features.
All of the following:
i. Prominent and persistent mood disturbance characterized by predominantly depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.
ii. Full criteria for major depressive-like episode are not met.
c. Mood disorder with manic features.
i. Prominent and persistent mood disturbance characterized by predominantly elevated, expansive, or irritable mood.
e. Mood disorder with mixed features.
i. Prominent and persistent mood disturbance characterized by symptoms of both depression and mania; neither predominates.
For all mood disorders:
Symptoms must cause significant distress or impairment in social, occupational, or other important areas of functioning.
Exclusions:
• Primary mental disorders.
• Substance-induced mood disorder.
• Adjustment disorder with depressed mood.

12. **Movement disorder (chorea)**
Chorea: Irregular, involuntary brief and unpredictable, jerky movements that may involve any portion of the body in random sequence.
Diagnostic criteria:
Both of the following:
a. Observed abnormal movements.
b. Random, unpredictable sequence of movements.

Exclusions:
• Wilson's disease.
• Huntington's disease (and other hereditary disorders).
• Medications (neuroleptics, oral contraceptives, phenytoin, L-DOPA, calcium channel blockers).
• Illicit drugs.

13. **Myasthenia gravis**

Neuromuscular transmission disorder characterized by fluctuating weakness and fatigability of bulbar and other voluntary muscles without loss of reflexes or impairment of sensation or other neurological function. Myasthenia gravis is an autoimmune disorder mediated by antibodies to acetylcholine receptors. It may occur with other diseases of immunological origin.

Diagnostic criteria:
a. Characteristic signs and symptoms include one or more of the following:
i. Diplopia, ptosis, dysarthria, weakness in chewing, difficulty in swallowing, muscle weakness with preserved deep tendon reflexes, and, less commonly, weakness of neck extension and flexion, and weakness of trunk muscles.
ii. Increased weakness during exercise and repetitive use with at least partially restored strength after periods of rest.
iii. Dramatic improvement in strength following administration of anticholinesterase drug (edrophonium and neostigmine).
And one or more of the following:
b. EMG and repetitive stimulation of a peripheral nerve: In myasthenia gravis, repetitive stimulation at a rate of two per second shows characteristic decremental response that is reversed by edrophonium or neostigmine. Single-fiber studies show increased jitter.
c. Antibodies to acetylcholine receptors.

Exclusions:
• Congenital myasthenic syndrome, progressive restricted myopathies, steroid and inflammatory myopathies, motor neuron disease.
• Multiple sclerosis, variants of Guillain-Barre syndrome (e.g., Miller-Fisher syndrome).
• Organophosphate toxicity, botulism, black widow spider venom.
• Eaton-Lambert syndrome.
• Stroke.
• Medications: neuromuscular blocking agents, aminoglycosides, penicillamine, antimalarial drugs, colistin, streptomycin, polymyxin B, tetracycline.
• Hypokalemia; hypophosphatemia.

Associations:
• Pure red cell aplasia.
• Thyroid abnormalities.
• Thymoma.

14. **Myelopathy**

Diagnostic criteria:
Usually rapid onset (hours or days) of one or more of the following:
a. Bilateral weakness of legs with or without arms (paraplegia/quadriplegia); may be asymmetric.
b. Sensory impairment with cord level similar to that of motor weakness, with or without bowel and bladder dysfunction.

Exclusions:
• Mass lesion causing compression of or within spinal cord (e.g., prolapsed disc, tumor, hematoma, or ruptured spinal arteriovenous malformation).
• *Cauda equina* lesion.

15. **Neuropathy, cranial**

Diagnostic criteria:
Syndrome corresponding to specific nerve function:
a. Olfactory nerve: loss of sense of smell, distortion of smell, and loss of olfactory discrimination.
b. Optic nerve: decrease or loss of visual acuity, diminished color perception, afferent pupillary defect, and visual field deficits.
c. Oculomotor nerve: ptosis of the upper eyelid and inability to rotate eye upward, downward, or inward (complete lesion), and/or dilated nonreactive pupil and paralysis of accommodation (interruption of parasympathetic fibers only).
d. Trochlear nerve: extorsion and weakness of downward movement of affected eye.
e. Abducens nerve: weakness of eye abduction.
f. Trigeminal nerve: paroxysm of pain in lips, gums, cheek, or chin initiated by stimuli in trigger zone (trigeminal neuralgia) and sensory loss of the face or weakness of jaw muscles.
g. Facial nerve: unilateral or bilateral paralysis of facial expression muscles, or impairment of taste, or hyperacusis (painful sensitivity to sounds).
h. Vestibulo-cochlear nerve: deafness, tinnitus (cochlear), dizziness, and/or vertigo (vestibular).
i. Glossopharyngeal nerve: swallowing difficulty, deviation of soft palate to normal side, anesthesia of posterior pharynx and/or glossopharyngeal neuralgia (unilateral stabbing pain in root of tongue and throat, triggered by coughing, sneezing, swallowing, and pressure on ear tragus).
j. Vagus nerve: soft palate droop, loss of the gag reflex, hoarseness, nasal voice, and/or loss of sensation at external auditory meatus.
k. Accessory nerve: weakness and atrophy of sternocleidomastoid muscle and upper part of trapezius muscle.
l. Hypoglossal nerve: paralysis of one side of tongue with deviation to the affected side.
Exclusions:
• Skull fracture.
• Tumor: meningioma, carcinomatous meningitis, aneurysm.
• Infection: herpes zoster, neuroborreliosis, syphilis, mucormycosis.
• Miller-Fisher syndrome.

16. **Plexopathy**
Disorder of brachial or lumbosacral plexus producing muscle weakness, sensory deficit, and/or reflex change not corresponding to the territory of single root or nerve.
Diagnostic criteria:
All of the following:
a. Characteristic signs and symptoms:
i. Brachial plexus: deep pain in shoulder, muscle weakness, sensory deficit and/or reflex impairment of arm, or
ii. Lumbosacral plexus: deep boring pain in thigh, muscle weakness, sensory deficit, and/or reflex impairment of leg.
b. Positive EMG finding (concentric needle examination) *and/or* nerve conduction studies for EMG: more than one root or nerve abnormalities with sparing of paraspinal muscles for nerve conduction study: absent or reduced amplitude on motor or sensory nerve conduction.
c. Normal MRI or CT scan (optional: myelogram) to rule out a higher neurological lesion.
Exclusions:
• Damage from injury, compression, tumor, aneurysm, radiation.
• Cervical rib, thoracic outlet syndrome.
• Plexus neuritis.
• Toxic: heroin.
• Infectious: Lyme disease, leprosy, herpes zoster.

17. **Polyneuropathy**

Acute or chronic disorder of sensory and motor peripheral nerves with variable tempo characterized by symmetry of symptoms and physical findings in a distal distribution.

Diagnostic criteria:

One or both of the following:

a. Clinical manifestations:

i. Clinical demonstration of distal sensory and/or motor deficit.

ii. Symmetry of signs/symptoms, and/or.

b. Confirmation by EMG:

i. Concentric needle examination demonstrating denervation of muscle, *or*

ii. Nerve conduction study demonstrating axonal or demyelinating neuropathy.

Exclusions:

• Vitamin deficiencies: B12, niacin, thiamine.

• Hypothyroidism.

18. **Psychosis**

Severe disturbance in the perception of reality characterized by delusions and/or hallucinations

Diagnostic criteria:

All of the following:

a. At least one of the following:

i. Delusions.

ii. Hallucinations without insight.

b. The disturbance causes clinical distress or impairment in social, occupational, or other relevant areas of functioning.

c. The disturbance does not occur exclusively during the course of a delirium.

d. The disturbance is not better accounted for by another mental disorder (e.g., mania).

Exclusions:

• Primary psychotic disorder unrelated to SLE (e.g., schizophrenia).

• Substance- or drug-induced psychotic disorder (including nonsteriodal anti-inflammatory drugs, antimalarials).

• Psychologically mediated reaction to SLE (brief reactive psychosis with major stressor).

19. **Seizures and seizure disorders**

Abnormal paroxysmal neuronal discharge in the brain causing abnormal function. Isolated seizures are distinguished from the diagnosis of epilepsy. Epilepsy is a chronic disorder characterized by an abnormal tendency for recurrent, unprovoked seizures that are usually stereotypic. Approximately 3% of the population has epilepsy. Typically, provoked seizures result from treatable conditions, such as sleep deprivation, toxic exposure to stimulants, withdrawal from narcotics, barbiturates, or alcohol, fever,
infection, metabolic disturbances, or SLE.

The approach to the evaluation of patients with a new-onset spell that may be a seizure, and the classification of seizures regardless of whether they are isolated seizures or part of a seizure disorder (e.g., epilepsy), are the same. The approach to treatment, however, is usually different. Although anticonvulsants are effective in controlling seizures acutely whether provoked or not, continuous prophylaxis is principally reserved for patients with epilepsy. Seizures may occur with or without the loss of consciousness. Seizures are divided into *partial* and *generalized*. Partial seizures have clinical or electroencephalographic evidence of a focal onset; the abnormal discharge usually arises in a portion of one hemisphere and may spread to the rest of the brain during a seizure. Primary generalized seizures have no interictal evidence of focal onset on electroencephalogram (EEG). A generalized seizure can be primary or secondary.

a. Primary generalized seizures (bilaterally symmetric and without local onset).

i. Tonic clonic (grand mal) or tonic or clonic.

ii. Atonic or astatic seizures.
iii. Absence seizures (petit mal).
Typical absences consist of abrupt onset and cessation of impairment of consciousness, with or without automatism, myoclonic jerks, tonic or autonomic components. A 3-Hz spike and wave discharge is usual EEG abnormality. Atypical absences have less abrupt onset and/or cessation of impaired consciousness and are more prolonged in tone with EEG abnormalities other than 3-Hz spike and wave discharge.
iv. Myoclonic seizures.
b. Partial or focal seizures (seizures beginning locally) (also referred to as Jacksonian, temporal lobe, or psychomotor seizure, according to type).
i. Simple, without impairment of consciousness. Depending on anatomic site of origin of seizure discharge, initial symptom may be motor, sensory, aphasic, cognitive, affective, dysmnesic, illusional, olfactory, or psychological..
ii. Complex, with partial impairment of consciousness, which may be simple at onset, followed by alteration or impairment of consciousness. Symptoms same as in i.
iii. Simple or complex may evolve to secondary generalized tonic/clonic seizures. Sometimes secondary generalization is so rapid that there is no clinical evidence of partial onset, only electroencephalographic.

Diagnostic criteria:

a. Independent description by a reliable witness.
b. EEG abnormalities.

Exclusions:

Seizure-like signs or symptoms or seizure from
• Vasovagal syncope.
• Cardiac syncope.
• Hysteria.
• Hyperventilation.
• Tics.
• Narcolepsy and cataplexy.
• Labyrinthitis.
• Alcohol and drug withdrawal.
• Medications: quinolones, imipenem.
• Subarachnoid hemorrhage.
• Trauma.
• Hypoglycemia.
• Panic attacks, conversion disorders, and malingering.

A study on 'NEUROPSYCHIATRIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS'

PROFORMA

No.	

Name: **Age/Sex**: **OP/IP No**:

Date:

Address: **Phone No:**

Complaints *(Neurological)*

Headache	:	☐
Involuntary movements	**:**	☐
Seizures	**:**	☐
Altered sensorium	**:**	☐
Weakness	**:**	☐
Muscle pain	**:**	☐
Numbness/parasthesias	:	☐
Cranial nerve symptoms	:	☐
Postural hypotension	:	☐
Hallucinations/delusions	:	☐
Others	**:**	☐

Complaints *(Non-Neurological)*

Joint pains	☐	**Rashes**	☐
Oral ulcers	☐	**Renal symptoms**	☐
Chest pain/dyspnoea/palpitation	☐	**others**	☐

ACR CRITERIA:

1. Malar rash .
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis

a. Pleuritis *OR*

b. Pericarditis

7. Renal disorder
8. Neurological disorder a. Seizures
9. Hematological disorder
10. Immunological disorder

a. Positive LE cell preparation *OR*

b. Anti-DNA: *OR*

c. Anti-Sm: *OR*

11. Antinuclear antibody

Laboratory Investigations:

Hb: **TC:** **DC: P- L- E-**

ESR: mm/hr

Blood urea: mg/dl **Serum creatinine:** mg/dl

Anti Nuclear Antibody:

dsDNA antibody:

Anti cardiolipin antibody:

Lupus Anticoagulant:

Imaging:

CT Brain:

MRI Brain:

MRI spinal cord:

CSF analysis:

Others:

Nerve Conduction Studies:

MOTOR NERVE CONDUCTION STUDY

NERVE	LATENCY **milli sec**		AMPLITUDE **mV**		NCV	F wave
	Distal	**Proximal**	**Distal**	**Proximal**	**m/s**	**milli sec**
Right Median						
Right Ulnar						
Left Median						
Left Ulnar						
Right Tibial						
Right Peroneal						
Left Tibial						
Left Peroneal						

SENSORY NERVE CONDUCTION STUDY

NERVE	LATENCY	AMPLITUDE	VELOCITY
Right Median			
Right Ulnar			
Left Median			
Left Ulnar			
Right Sural			
Left Sural			

ELECTROMYOGRAPHY(EMG):

ELECTROENCEPHALOGRAPHY(EEG):

NEUROPSYCHIATRIC : ACR NOMENCLATURE

1. **Acute confusional state**
2. **Acute inflammatory demyelinating polyradiculoneuropathy**
3. **Anxiety disorder**
4. **Aseptic Meningitis**
5. **Autonomic disorder**
6. **Cerebrovascular disease**
7. **Cognitive Dysfunction**
8. **Demyelinating syndrome**
9. **Headache**
10. **Mononeuropathy (single/multiplex)**
11. **Mood disorders**
12. **Movement disorder**
13. **Myasthenia gravis**
14. **Myelopathy**
15. **Neuropathy, cranial**
16. **Plexopathy**
17. **Polyneuropathy**
18. **Psychosis**
19. **Seizures and seizure disorders**

TREATMENT

Drugs given:

Duration of hospital stay:

19	CHRISTINA	4	11	29							Y			Y											Right
20	REVATHI	4	29	26									Y		Y										norm
21	SAMSHAD BEGUM	6	26	30											Y						Y				Axona
22	SASI	4	7	29									Y												norm
23	PARVATHI	4	3	12																		Y			norm
24	JASMINE	5	32	30									Y		Y								Y	Y	norm
25	VALLI	4	5	30												Y									norm
26	NANDHINI	4	11	30																			Y		norm
27	SAKTHI	4	19	0	Y					Y	Y		Y		Y								Y		norm
28	PAULRAJ	4	9	29										Y											Monon
29	BRINDHA	4	5	27		Y																			AIDP
30	PRIYA	4	40	28									Y		Y								Y		norm
31	SHALINI	5	7	30									Y												norm
32	SARASWATHY	4	3	30																					norm
33	SUNDARI	5	5	30																				Y	norm
34	BHARATHI	7	29	27									Y		Y									Y	norm
35	PRITHIMA	4	30	20											Y										norm
36	BARGHAVI	4	9	16																		Y			norm
37	SOPHIA	4	21	12									Y		Y								Y		norm
38	HAMSAVENI	4	4	11																		Y			norm
39	KANCHANA	4	2	20												Y									norm
40	VIJAYALAKSHMI	5	22	30									Y		Y								Y		norm
41	INDIRA	4	29	30									Y		Y										norm
42	ISHTIAQ	4	11	29									Y												norm